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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 16 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PRALLE® (IMIPROTHRIN; S-41311)**: Request for Registration for Non-food Use -- Review of Toxicity Database

DP BARCODE: D222183; D224685
Submission No.: S498997
P.C. Code: 004006
MRID No.: 43750718 through 43750737; 43750740; 43769702 and 43769703

FROM: Sanjivani Diwan, Ph.D. Sanjivani Diwan 8/1/96
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Debbie McCall/Steve Robbins
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Yiannakis M. Ioannou, Ph.D. Y.M. Ioannou 8/1/96
Acting Branch Chief
Toxicology Branch II
Health Effects Division (7509C)

Registrant: Sumitomo Chemical Company, Ltd., Japan

Action Requested: Review of toxicology data to support registration for PRALLE® (Imiprothrin or S-41311), a new synthetic pyrethroid insecticide, for indoor, non-food use.

Recommendation: Toxicology Branch II has determined that the Toxicology database on PRALLE® (≥92.9% a.i.) and its Manufacturing Use Product (50% formulation) is adequate to support registration for spot treatment in cracks and crevices for the control of crawling insects.

Background:

Sumitomo Chemical Company, Ltd. has submitted a request for registration of S-41311 (PRALLE®) for indoor, non-food use. The proposed end use product will consist of 0.4% (w/w) S-41311 in a 9-ounce (255 grams) aerosol can of water-based formulation. This formulation will contain 1.02 grams (0.0022 lbs) of S-41311. The Registrant proposes using this formulation at concentration of 0.08 lbs of active ingredient (a.i.) per gallon. This pesticide will be applied in the crack/crevice treatment for control of crawling insects such as cockroches.

Review of Toxicology Data on Technical Material - S-41311

Acute Toxicity Studies (Guideline §81-1 through 81-6):

- Oral LD_{50} - Rat (MRID No.: 43750718).

  Male and female (5/sex/group) Crj:CD rats were orally administered 1-5 mL/kg b.w. of undiluted S-41311 at dose levels of 0, 500, 700 (females only), 1000, 1400, 2000, 2800, or 4000 (males only) mg/kg. The acute oral LD_{50} for S-41311 was 1800 mg/kg for males and 900 mg/kg for females.

  Toxicity Category III; the study is classified as Acceptable

- Dermal LD_{50} - Rat (MRID No.: 43750720)

  Male and female (5/sex) Crj:CD rats received dermal application of S-41311 at a dose of 2000 mg/kg for 24 hours. The acute dermal LD_{50} for S-41311 was greater than 2000 mg/kg.

  Toxicity Category III; the study is classified as Acceptable

- Inhalation LC_{50} - Rat (MRID No.: 43750722)

  Male and female (5/sex/group) Sprague-Dawley rats were exposed to an atmospheric concentration of 0.418 or 1.2 mg/l of S-41311 for four hours. The acute inhalation LC_{50} for S-41311 was >1.2 mg/l for male and female rats.

  Toxicity Category III; the study is classified as Acceptable.

- Primary Eye Irritation - Rabbit (MRID No.: 43750724)

  0.1 mL of undiluted S-41311 was instilled into the conjunctival sac of

one eye of each of six New Zealand white rabbits (3/sex). The treated eyes were left unwashed post-instillation. The other eye served as an untreated control. The study demonstrated that S-41311 was non-irritating to rabbit eye.

Toxicity Category IV; the study is classified as Acceptable

- Primary Skin Irritation - Rabbit (MRID No.: 43750724)

  0.5 mL of undiluted S-41311 was topically applied to a clipped skin area of each of six New Zealand white rabbits (3/sex) for four hours. The study demonstrated that S-41311 is non-irritating to the rabbit skin.

  Toxicity Category IV; the study is classified as Acceptable.

- Skin Sensitization - Guinea pig (MRID No.: 43750726) using Magnusson and Kligman test.

  A group of 20 male Hartley guinea pigs received three intradermal injections (5% and 10% S-41311) and dermal application (25% S-41311) during the induction phase; a topical challenge dose of 25% S-41311 was administered to animals. The positive control group (5 males) received DNCB intradermally (0.05% and 0.1%) and dermally (0.5%) during induction phase and a challenge dose of 0.5% DNCB.

  Mild sensitizer; the study is classified as Acceptable.

- Skin Sensitization - Guinea pig (MRID No.: 43750727) using the Buehler method.

  A group of ten male Hartley albino guinea pigs received three induction doses of 25% S-41311 in corn oil and a challenge application of 25% S-41311 in corn oil. The positive control group (5 males) received DNCB during induction phase (1% in acetone) and challenge phase (0.5% DNCB).

  Not a sensitizer; the study is classified as Acceptable.

Genotoxicity: With the exception of Chinese Hamster Lung cell assay, S-41311 was found to be non-genotoxic in a battery of assays.

- Microbial Gene Mutation Assay - Salmonella typhimurium (MRID No.: 43750734)

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No evidence of mutagenic response was noted in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and Escherichia coli strain WP2 uvrA at doses ranging from 156 to 5000 μg/plate S-41311 in both the presence and absence of S9 activation. The study is classified as Acceptable.

- Mammalian cell cytogenetic assay - Chinese hamster lung cells (MRID No. 43750735)

  In the absence of S9 activation (at doses of 50-200 μg/mL and 75-300 μg/mL), there was no evidence of clastogenicity. Overall the data provide clear evidence that S9-activated S-41311 (95.3%)is clastogenic at doses of 25-100 μg/mL. The study is classified as acceptable.

- Micronucleus assay - Mouse (MRID No.: 43750736),

  There was no evidence of a cytotoxic, clastogenic or aneugenic effect at any dose (at 19, 38 or 75 mg/kg/day S-41311 (95.3%) or sacrifice time. The study is classified as Acceptable.

- In Vivo/In Vitro Unscheduled DNA synthesis (UDS) Assay - Rats (MRID No. 43750737)

  No evidence of either a cytotoxic or genotoxic response at any dose (250, 500 or 1000 mg/kg S-41311; 95.3%) or sacrifice time. The study report is, however, incomplete because primary data were not provided. The study is Unacceptable but is upgradable.

- Mammalian cell gene mutation assays (MRID No. 43769703)- Chinese hamster lung fibroblasts V79 cells

  No evidence of mutagenicity was observed over dose ranges of 44.4-150 μg/mL -S9 or 50-200 μg/mL +S9 S-41311 (95.3%). The study is classified as Acceptable.

21-Day Dermal Subchronic Toxicity - Rat (Guideline §82-2; MRID # 43750740)

Sprague-Dawley rats (5/sex/group) were treated topically with dosages of either 100, 300 or 1,000 mg/kg of S-41311 (92.9%) (2 ml/kg/day) to approx. 5 x 5 cm shaved area, 6 hours per day for 21 consecutive days. The systemic toxicity LOEL is 1000 mg/kg for males and females based on decrease in body weight gain; the systemic toxicity NOEL is 300 mg/kg for males and females.

The dermal toxicity LOEL is 1,000 mg/kg for males and females based on

acanthosis and hyperkeratosis of the skin; the dermal toxicity NOEL is 300 mg/kg for males and females. The study is classified as Acceptable.

Subchronic Inhalation Toxicity - Rat (§82-4; MRID # 43750730).

Sprague-Dawley rats (10/sex/dose) were exposed by whole body exposure to S-41311 (92.5%) mist aerosol at analytical concentrations of 0, 2.4, 22.0, and 186 mg/m^3 (0, 0.0024, 0.022, and 0.186 mg/l, respectively) for 4 hours/day, 5 days/week for a total of 28 days for males and 29 days for females. The two control groups were exposed to vehicle or air. The LOEL is 186 mg/m^3, based on increased incidence of clinical signs indicating effects on the nervous system, decreases in body weight gain, hemolytic anemia, increase in relative liver weights, dark liver, increase in absolute and relative salivary gland weights and hyperplasia of acinous cells. The NOEL is 22 mg/m^3. The study is classified as Acceptable.

Subchronic Oral Toxicity - Rat (§82-1a; MRID # 43769702).

Sprague-Dawley rats (12/sex/dose) were treated at dosage levels of 0, 100, 3,000, 6,000, and 10,000 ppm S-41311 (92.5%) (0, 5.9, 178.6, 350.4 or 611.2 mg/kg/day in males and 6.7, 196.6, 399.0 or 657.0 mg/kg/day in females, respectively) for three months. The LOEL is 3,000 ppm (178.6 mg/kg/day in males and 196.6 mg/kg/day in females) based on decreases in body weight gain, food consumption and hemolytic anemia. The NOEL for both sexes is 100 ppm (5.9 and 6.7 mg/kg/day in males and females, respectively). The study is classified as Acceptable.

Developmental Toxicity - Rabbit (Guideline §83-3b; MRID# 43750731; 43750733)

The developmental toxicity of S-41311 (≥92.2%) in JW-NIBS rabbits was investigated in two phases.

During phase I, S-41311 was administered by gavage to pregnant rabbits (10/dose) at dose levels of 0, 30, 100 and 300 mg/kg/day from gestational days (GD) 6 to 18, inclusive.

Phase II was conducted to establish the NOEL for developmental toxicity. During this phase, S-41311 was administered by gavage to groups of pregnant rabbits (20/group) at dose levels of 0, 3, 10, or 30 mg/kg/day from GD 6–18, inclusive.

The combined results of the two phases of the study established the maternal LOEL at 100 mg/kg/day, based on decrease in body weight gain and food

consumption. The maternal NOEL is 30 mg/kg/day. The developmental LOEL is 100 mg/kg/day, based on the findings of lower mean fetal body weights, fusion of nasal bones, hypoplasia of the frontal bone and increased incidence of 27th pre-sacral vertebrae. Developmental toxicity NOEL is 30 mg/kg/day. The study is classified as Acceptable.

Review of Toxicity Data on End-Use-Product - S-41311 MUP (a 50% formulation): The Registrant also submitted seven acute toxicity studies with formulation. The following summarizes the conclusions of the studies:

Acute Toxicity Studies (Guideline §81-1 through 81-6)

- Oral LD_{50} - Rat (MRID No.: 43750719).

  Male and female Crj:CD rats (5/sex) were orally administered 1-5 mL/kg b.w. of undiluted S-41311 MUP at dose levels of 0, 1000, 2000, 2600 (females only), 3200, 4000, or 5000 (males only) mg/kg. The acute oral LD_{50} for S-41311 MUP was 4500 mg/kg for males and 2400 mg/kg for females.

  Toxicity Category III; the study is classified as Acceptable

- Dermal LD_{50} - Rat (MRID No.: 43750721), Crj: CD rats (5/sex) each received dermal application of S-41311 MUP at a dose of 2000 mg/kg for 24 hours. The acute dermal LD_{50} for S-41311 MUP in male and female rats was greater than 2000 mg/kg.

  Toxicity Category III; the study is classified as Acceptable

- Inhalation LC_{50} - Rat (MRID No.: 43750723)

  Sprague-Dawley rats (5/sex/group) were exposed whole-body to mist aerosols at concentrations of 2.81, 3.62 or 4.43 mg/l of S-41311 50% MUP for four hours. The estimated LC_{50} values were between 3.62–4.43 mg/L for males and 2.81– 3.62 mg/L for females. The acute inhalation LC_{50} for S-41311 50% MUP in male and female rats was >2 mg/l (limit dose).
  Toxicity Category IV; the study is classified as Acceptable.

- Primary Eye Irritation - Rabbit (MRID No.: 43750725)

  0.1 mL of undiluted S-41311 MUP was instilled into the conjunctival sac of one eye of each of six New Zealand white rabbits (3/sex). The other eye served as an untreated control. The study demonstrated that S-

41311 MUP was non-irritating to rabbit eye.

Toxicity Category IV; the study is classified as Acceptable.

- Primary Skin Irritation - Rabbit (MRID No.: 43750725)

  0.5 mL of undiluted S-41311 MUP was topically applied to a clipped skin area of each of six New Zealand white rabbits (3/sex) for four hours. The treated areas were examined for signs of dermal irritation (edema and erythema) and scored after 30 minutes and at 24, 48 and 72 hours post-treatment. No evidence of erythema or edema was observed in treated rabbits at any of the time points following treatment. The study demonstrated that S-41311 MUP is non-irritating to the rabbit skin.

  Toxicity Category IV: The study is classified as acceptable.

- Skin Sensitization - Guinea pig (MRID No.: 43750729) using Magnusson and Kligman test.

  A group of 20 male Hartley guinea pigs received intradermal injections (5% and 10% S-41311 MUP) and dermal application (undiluted S-41311 MUP) during the induction phase and 5% and 25% S-41311 MUP during challenge phase. The positive control group (5 males) received DNCB intradermally (0.05% and 0.1%) and dermally (0.5%) during induction phase and a dose of 0.5% during challenge phase.

  Not a sensitizer; the study is classified as Acceptable.

- Skin Sensitization - Guinea pig (MRID No.: 43750728) using the Buehler method

  A group of ten male Hartley albino guinea pigs received three topical induction doses of undiluted S-41311 MUP and a challenge application of 0.5 ml undiluted S-41311 MUP. The positive control group (5 males) received DNCB during induction phase (1% in acetone) and challenge phase (0.5% DNCB in acetone).
  Not a sensitizer; the study is classified as Acceptable.

Proposed Labelling

Based on the review of acute toxicity studies with technical imiprothrin and its 50% formulation, all studies met the criteria for Toxicity Category III or IV. The proposed

label accurately reflects the toxicity of S-41311 and bears the signal word "CAUTION".

Toxicology Profile for S-41311 and its Formulation:

a. Data requirements to support registration of S-41311 (Non-food use)

Studies submitted	Required	Satisfied
81-1 Acute oral - rat	yes	yes
81-2 Acute dermal - rat	yes	yes
81-3 Acute inhalation - rat	yes	yes
81-4 Primary eye irritation - rabbit	yes	yes
81-5 Primary dermal irritation - rabbit	yes	yes
81-6 Dermal sensitization - guinea pig	yes	yes
82-1 Subchronic feeding (rats)	yes	yes
82-2 21-Day dermal	yes	yes
82-4 Subchronic inhalation	yes	yes
83-3 Developmental toxicity - rat	No	n/a
83-3 Developmental toxicity - rabbit	yes	yes
84-2(a) Mutagenicity	yes	yes
84-2(b) Mutagenicity	yes	yes
84-4 Mutagenicity	yes	yes

a. Data requirements to support registration of 50.5% formulation (Non-food use)

Studies submitted	Required	Satisfied
81-1 Acute oral - rat	yes	yes
81-2 Acute dermal - rat	yes	yes
81-3 Acute inhalation - rat	yes	yes
81-4 Primary eye irritation - rabbit	yes	yes
81-5 Primary dermal irritation - rabbit	yes	yes
81-6 Dermal sensitization - guinea pig	yes	yes

Toxicology Issues

1. RfD

The data for S-41311 was presented to the RfD/Peer review Committee for consideration on 09/19/96. The Committee recommended lowering the NOEL from 1,000 mg/kg/day to 300 mg/kg/day based on decrease in body weight gain at 1,000 mg/kg/day (HDT) observed in a 21-day dermal toxicity study in rats. Based on the proposed use pattern, the Committee recommeded not to establish an RfD for this chemical at this time.

2. Carcinogenicity

There are no carcinogenicity studies available for assessment. The results of five mutagenicity studies were negative. These studies were acceptable and fulfill guidelines 84–2a and 84–4.

3. Toxicology data gaps - None.

Updated One-liners

Attached are updated one-liners to support the data requirements.

Conclusions/Recommendations

Based on the review of the toxicology data, Toxicology Branch II has determined that the data base for S-41311 is adequate to support the registration for indoor, non-food use in cracks and crevices for the control of crawling insects.

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S-41311 Acute Oral Toxicity (81-1)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy, Date 7/17/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral Toxicity- Rat OPPTS 870.1100 [§81-1]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750718 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 (95.3%) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0026
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Single-dose Oral Toxicity Study of S-41311 in Rats
AUTHOR:	Y. Misaki
REPORT ISSUED:	May 22, 1992

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 43750718), groups of five male and five female Crj:CD rats were orally administered 10 mL/kg b.w. of S-41311 at dose levels of 0, 500, 700 (females only), 1000, 1400, 2000, 2800, or 4000 (males only) mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. Mortalities occurred at dose levels of ≥1000 mg/kg in males and ≥700 mg/kg in females. Clinical signs of toxicity were observed at these dose levels in both sexes within 30 minutes following administration and disappeared within 3 days in survivors. These included decreased spontaneous activity, prone position, lateral position, tremor, ataxic gait, irregular respiration, excretion of oily substance, urinary incontinence, and stained fur. Animals that died exhibited tremors and irregular respiration and died within 1/2-1 hour post-dosing. Transient supression of body weight gain was noted at ≥500 mg/kg in males and at ≥1000 mg/kg in females. **The acute oral LD_{50} for S-41311 was 1800 mg/kg for males and 900 mg/kg for females.**

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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I. MATERIALS

A. Test Material

Name: S-41311
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: No information available
Purity: 95.3%
Lot No.: LO-910802B
Stability : No information available

For dosing, the test formulation was dissolved in corn oil at concentrations of 50-400 mg/mL and administered (10 mL/kg) by plastic syringe; the control group was given corn oil at rate of 10 mL/kg body weight.

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Company, Ltd., Japan
Age: 6 weeks at the start of the study
Weight: Males - 221 to 242 g; Females - 152 to 171 g when dosed
Housing: 2-3 rats of the same sex in aluminum cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum* except for 4 hours after dosing
Acclimation Period: Quarantine over 7 days and acclimatized over 2 days

II. METHODS

Food was witheld from the animals for about 20 hours prior to dosing. Groups of five male and five female rats were dosed with 10 mL/kg b.w. of test compound in corn oil via gavage at dose levels of 500, 700 (females only), 1000, 1400, 2000, 2800 or 4000 (males only) mg/kg. The doses were administered using a plastic syringe (2 mL) with a flexible catheter attached. The control animals received corn oil. The animals were observed for mortality and clinical signs of toxicity at approximately 10 and 30 minutes, 1, 2, and 4 hours after dosing and once daily for the remainder of the 14-day observation period. Body weights were recorded prior to dosing, on days 1, 3, 5, 7, 10 and 14 post-dosing, and at death. At the end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

Mortalities occurred at ≥1000 mg/kg in males and at ≥700 mg/kg in females. The LD50 value was 1800 mg/kg (95% Confidence Limit: 1300 to 2480 mg/kg) for males and 900 mg/kg (95% Confidence Limit: 630 to 1280 mg/kg) for females. Clinical signs of toxicity were observed in males receiving ≥1000 mg/kg and females receiving ≥700 mg/kg. These were noted beginning at 30 minutes following dosing and disappeared within 3 days. These consisted of decreased spontaneous activity, tremor, prone or lateral position, ataxic gait, irregular respiration, urinary incontinence, and stained fur. The body weight gain was significantly lower compared to controls in males at 500 and 1400 mg/kg on Day 1 and at 2000 and 2800 mg/kg on Days 1, 3, 5, and 10; in females it was significantly lower at 1000 and 1400 mg/kg on Day 1 only. Gross necropsy of dead animals revealed oily material in the stomach and autolysis of the intestine; no remarkable treated-related findings were noted during necropsy of surviving animals. The acute oral LD_{50} was 1800 mg/kg for males and 900 mg/kg for females.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute oral LD_{50} for S-41311 in rats was 1800 mg/kg for males and 900 mg/kg for females.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

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S-41311 Acute Dermal Toxicity (81-2)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan, Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D. M.P.H. Virginia A Dobozy 7/17/96, Date
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity- Rat OPPTS 8700.1200 [§81-2]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750720 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 (95.3%) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0027
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Single-dose Dermal Toxicity Study of S-41311 in Rats
AUTHOR:	Y. Misaki
REPORT ISSUED:	May 22, 1992

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 43750720), five male and five female Crj: CD rats each received dermal applications of S-41311 in corn oil at a dose of 2000 mg/kg for 24 hours. A control group received dermal applications of corn oil alone. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There were no mortalities, clinical signs of toxicity, body weight changes or gross pathology observed in either sex. **The acute dermal LD_{50} for S-41311 in male and female rats was greater than 2000 mg/kg.**

The study is classified as Acceptable with a Toxicity Category III and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rats.

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S-41311 Acute Dermal Toxicity (81-2)

I. MATERIALS

A. Test Material

Name: S-41311
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: No information available
Purity: 95.3%
Lot No.: LO-910802B
Stability: No information avaiolable

The test material was dissolved in corn oil at a concentration of 400 mg/ml prior to dosing.

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Company, Ltd., Japan
Age: 6 weeks at the start of the study
Weight: Males - 253 to 283 g; Females - 178 to 195 g when dosed
Housing: 2-3 rats of the same sex in aluminum cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum*
Acclimation Period: Quarantine over 7 days and acclimatized over 2 days

II. METHODS

One day prior to dosing, the backs of all the animals were clipped, exposing an area of approximately 10% of the total body surface. On the day of dosing, a dose (5 mL) of 2000 mg/kg of test material was applied on the shaved area (30 cm^2) on the skin using a plastic syringe (2 mL). The treated area was covered with a gauze patch which was secured with a surgical tape wrapped around the trunk. Twenty-four hours after the application, the treated skin was wiped with cotton dipped in diethyl ether to assess the skin reaction. The control group received 5 mL/kg corn oil in the same manner. The animals were observed for mortality and clinical signs of toxicity at approximately 10 and 30 minutes, 1, 2, and 4 hours after dosing and once daily for the remainder of the 14-day observation period. Body weights were recorded prior to dosing, on days 1, 3, 5, 7, 10 and 14 days post-dosing, and at death. At the

end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

The amount of test substance/area covered approximately 10% of the body surface area. No mortalities and clinical signs of toxicity were observed. Therefore, the estimated LD50 value was greater than 2000 mg/kg for male and female rats. There were no treatment-related changes in body weight gain in either sex. There were no dermal reactions at the site of application. At necropsy, no treatment-related findings were noted. The acute dermal LD_{50} was greater than 2000 mg/kg.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute dermal LD_{50} for S-41311 in male and female rats was greater than 2000 mg/kg.

The study is classified as Acceptable with a Toxicity Category III and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rats.

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S-41311 Acute Inhalation Toxicity (81-3)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/30/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy Date 7/30/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation Toxicity- Rat OPPTS 8700.1300 [§81-3]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750722 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 (92.9%) Synonym: Imiprothrin
STUDY NUMBER:	SGT-10-0003
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	A Single-dose Inhalation Toxicity Study of S-41311 in Rats
AUTHOR:	S. Kawaguchi
REPORT ISSUED:	August 10, 1991

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 43750722), five male and five female Sprague-Dawley rats per group were exposed whole-body to atmospheric concentrations of 0.418 or 1.20 mg/l of S-41311 for four hours. The animals were observed for 14 days. No mortalities were noted. Clinical signs were not monitored during exposure due to high concentrations of test aerosols. Clinical signs of toxicity were observed in both sexes at 0.418 mg/L one hour post-exposure and included irregular respiration, wet fur, dark red substance around snout, tip toe gait, urinary incontinence and rough coat. Additional signs noted at 1.2 mg/L in males and/or females included hypersensitivity, ataxic gait, dark red substance around eyes, and loss of abdominal and submandibular hair. These signs disappeared by Day 9 with the exception of loss of hair which improved after Day 13 of the observation period. The body weight gain was lower in males at 0.418 mg/L on Day 3 and at 1.20 mg/L on Day 7. No treatment-related gross pathological findings were observed. The mean nominal concentrations were 2.52 and 9.31 mg/L for the atmospheric concentrations of 0.418 and 1.20 mg/L, respectively.

The MMAD of mist particles (for the 1.20 mg/L dose) was less than <3 μm (range: 0.77-0.84 μm); the Log-standard Geometric Deviation range was 1.61-1.76.

The acute inhalation LC_{50} for S-41311 (92.9%) was >1.20 mg/l for male and female rats.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-3) for an acute inhalation toxicity study in rats.

I. MATERIALS

A. Test Material

Name: S-41311
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: Clear, yellow-orange oily liquid
Purity: 92.9%
Lot No.: Y-011001
Stability of compound: Test material was stable at room temperature

Test material was heated at 60-70^0 C and diluted in corn oil.

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Japan, Inc.
Age: 4 weeks at the start of the study
Weight: Males - 204 to 243 g; Females - 151 to 184 g when dosed
Housing: 2-3 rats of the same sex in aluminum cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum* except during dosing and until 4 hours after dosing
Acclimation Period: Quarantine over 7 days and acclimatized for 11 days

II. METHODS

Exposure Chamber

A five-compartment wire-mesh cage (floor space: 215 cm^2; height: 14 cm) was placed in an exposure chamber. The exposure chamber had a volume of 0.52 m^3. During exposure, five rats were housed in each cage (1 rat/compartment).

Atmosphere Generation and Monitoring

Food and water were withheld from the animals during exposure period. The animals were exposed to the test article aerosols by whole-body exposure. The dilutions of S-41311 in corn oil were pumped using a tube pump (TPC-5) into an atomizer (AKI Jet 04) and sprayed under compressed air. The aerosols were delivered to the exposure chamber; the chamber air was led to the exhaust port at a rate of 115 L/min and the pressure inside the chamber was maintained at a constant level. During exposure period, the temperature, relative humidity, air flow rate and pressure were

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monitored at the start of exposure and at 30 minutes as well as at 1, 2, 3, and 4 hours thereafter. A diagram of the test system is attached to the DER.

Analytical Chemistry

The concentration of the chemical in the test atmosphere was determined by gas chromatography at 1 and 3 hours after the start of exposure. Samples were collected through the sampling line of the chamber in a glass column packed with silica gel and a total of 100 L of chamber air samples was collected at a rate of 20 L/min using an air-sampler (D-80 RG) equipped with a flow meter. S-41311, collected on silica gel and extracted with acetone, was quantified by gas chromatography. The actual test concentration in the chamber was calculated using the value obtained from the analysis and the amount of air collected. The nominal test concentrations were obtained by dividing the total volume of the test aerosol consumed during exposure with the total amount of air flow into the chamber (115 l/min x 240 min.= 27.6 m^3).

Time to equilibrium was 4 minutes.

Particle Size Distribution

A microscopic sedimentation analyzer (SA-M1D) was used to determine the particle size distribution of the test atmosphere five times/group between 50 and 81 minutes after the start of exposure. The mean MMAD (median aerodynamic diameter) of the mist particles and LSD (Log-standard geometric deviation) were estimated using Probit analysis.

Animal Treatment

Groups of five male and five female rats received 4-hour whole-body exposure to corn oil (Group 1) or air alone (Group 2); Groups 3 and 4 were exposed to test concentrations of 0.418 and 1.20 mg/L, resepctively. Observations for mortality and clinical signs of toxicity were made at 30 minutes and hourly intervals during exposure and after exposure on day 1 (up to 4 hours), and then once daily during the 14-day observation period. The animals were weighed prior to exposure and at 3, 7 and 14 days following the exposure. At the end of the study, all the surviving animals were sacrificed and necropsied.

III. RESULTS

The calculated nominal aerial concentrations of S-41311 were 2.52 (Group 3) and 9.31 mg/L (Group 4) for groups exposed to actual aerial concentrations of 0.418 and 1.20 mg/L, respectively. The MMAD of mist particles ranged between 0.74-0.81 μm (Group 3) and 0.77-0.84 μm (Group 4); the Log-standard Geometric Deviation (LSD) range was 1.57-1.72 (Group 3) and 1.61-1.74 (Group 4).

No deaths occurred. The LC_{50} value was estimated to be >1.20 mg/L for both sexes. Because of high concentration of aerosols, the

clinical observations could not be made during exposure period. Following one hour after the exposure wet fur was noted in animals. Clinical signs of toxicity observed in both sexes, at 0.418 mg/L at one to four hours post-exposure, included irregular respiration, tip toe gait, ataxic gait (females), urinary incontinence and dark material around snout. These signs disappeared by day 3. Rough coat was observed in both sexes from days 3 to 6. Additional signs noted at 1.20 mg/L consisted of hypersensitivity and dark substance around eyes. Rough coat and loss of abdominal and submandibular hair were observed in females from day 7; the later finding tended to improve from day 13. In males at 0.418 mg/L, the body weight gain was lower compared to controls on day 3 and at 1.20 mg/L on days 7. However, the body weight gain returned to normal thereafter. No treatment-related gross or microscopic pathological findings were noted at necropsy.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute inhalation LC_{50} for S-41311 was >1.20 mg/L for male and female rats.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-3) for an acute inhalation toxicity study in rats.

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Imidacloprid

Page 22 is not included in this copy.

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_____ A draft product label.

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012119

S-41311 Primary Eye Irritation Study (81-4)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Virginia a Dabozzi 7/17/96, Date:
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation- Rabbit OPPTS 8700.2400 [§81-4]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750724 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 (95.3%) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0013
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Primary Eye and Skin Irritation Tests of S-41311 in Rabbits
AUTHOR(S):	T. Nakanishi
REPORT ISSUED:	February 12, 1992

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID # 43750724), 0.1 mL of undiluted Imiprothrin (95.3% a.i.) was instilled into the conjunctival sac of one eye of each of six New Zealand white rabbits (3/sex). The treated eyes were left unwashed post-instillation. The other eye served as an untreated control. The eyes were examined for signs of irritation and scored at 1, 24, 48 and 72 hours. One hour following application, a slight redness and very slight chemosis in conjunctiva were observed which were reversed after 48 hours. **The study demonstrated that S-41311 was non-irritating to rabbit eye.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-4) for a primary eye irritation study in rabbits.

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I. MATERIALS

A. Test Material

Name: S-41311
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate,
Synonym: Imiprothrin
Description: Viscous liquid
Purity: 95.3%
Lot No.: LO-910802B
Stability: No information available

B. Test Animals

Species: New Zealand white rabbits
Source: Kitayama LABES, Kyoto, Japan
Age: 10 weeks
Weight: Males and Females- 2.20-2.60 kg at dosing
Housing: Individually in aluminum cages
Environmental Conditions: Temperature: 22±2^{0}C
Relative Humidity: 55±15%
Photoperiod: 12 hours light
Air Changes: ≥10/hour
Food and Water: 100 g/day of RC-4 diet from Oriental Yeast Co., Ltd, Tokyo and water *ad libitum*
Acclimation Period: 14 days quarantine period followed by 10 days of acclimation

II. METHODS

During acclimation period, the eyes of rabbits were examined. On the day of dosing, 0.1 mL of the undiluted test material, warmed in warm water, was instilled in to the conjunctival sac of one eye of each animal. The other eye served as an untreated control. The eyes were left unwashed post-instillation. They were examined for evidence of irritation and scored at 1, 24, 48 and 72 hours. A copy of the Draize grading scale is attached to the DER. The irritation potential was determined by the method of Kay and Calandra (1962; see attachment).

III. RESULTS

One-hour following treatment, slight redness (grade 1) in conjunctiva was observed in all 6 rabbits and a very slight chemosis (grade 1) was noted in 2 males and 3 females. These signs disappeared after 48 hours. Using Kay and Calandra method (1962), the maximum mean score calculated for irritant reactions within 72 hours was 3.7; this was based on the effects observed one hour post-application. This score suggests that S-41311 was practically non-irritating to rabbit eye.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that S-41311 was non-irritating to rabbit eye.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-4) for a primary eye irritation study in rabbits.

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Confidential Statement of Formula

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S-41311 Primary Dermal Irritation Study (81-5)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan, Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/17/96, Date
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation- Rabbit OPPTS 8700.2500 [§81-5]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750724 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 (95.3%) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0013
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Primary Eye and Skin Irritation Tests of S-41311 in Rabbits
AUTHOR(S):	T. Nakanishi
REPORT ISSUED:	February 12, 1992

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 43750724), 0.5 mL of undiluted S-41311 (95.3% a.i.) was topically applied to a clipped skin area of each of six New Zealand white rabbits (3/sex) for four hours. The treated areas were examined for signs of dermal irritation (edema and erythema) and scored after 30 minutes and at 24, 48 and 72 hours post-treatment. No evidence of erythema or edema was observed in treated rabbits at any of the time periods. **The study demonstrated that S-41311 is non-irritating to the rabbit skin.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for a primary dermal irritation study in rabbits.

I. MATERIALS

A. Test Material

Name: S-41311
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: No information available
Purity: 95.3%
Lot No.: LO-910802B
Stability of compound: No information available

B. Test Animals

Species: New Zealand white rabbits
Source: Kitayama LABES, Kyoto, Japan
Age: 10 weeks
Weight: Males and Females - 2.20-2.60 kg at dosing
Housing: Individually in aluminum cages
Environmental Conditions: Temperature: 22±2°C
Relative Humidity: 55±15%
Photoperiod: 12 hours light
Air Changes: ≥10/hour
Food and Water: 100 g/day of RC-4 diet from Oriental Yeast Co., Ltd, Tokyo and water *ad libitum*
Acclimation Period: 14 days quarantine period followed by 10 days of acclimation

II. METHODS

Approximately 24 hours before treatment, the dorsal fur of each rabbit was clipped (the area size was not specified). On the day of dosing, 0.5 ml of the test material, warmed in warm water and then impregnated on a lint patch (2.5 x 2.5 cm), was applied to the clipped dorsal skin and secured in place with a surgical tape. At the end of the 4-hour exposure, the patches were removed and the treated sites were wiped with cotton soaked in acetone. The areas were examined for signs of dermal irritation and scored after 30 minutes and at 24, 48 and 72 hours post-application. A copy of the Draize grading scale is attached to the DER. The skin irritation potential was determined from the primary skin irritation score obtained.

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III. RESULTS

No skin reactions were observed in treated rabbits at any of the observation periods. The primary skin irritation score was 0.0. The study demonstrated that S-41311 was non-irritating to the rabbit skin.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that S-41311 is non-irritating to the rabbit skin.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for a primary dermal irritation study in rabbits.

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Confidential Review

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012119

S-41311 Dermal Sensitization Study (81-6)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 6/6/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y M Ioannou, Date: 6/6/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization - Guinea Pig
OPPTS 8700.2600 [§81-6]

DP BARCODE: D222183
P. C. CODE: 004006
SUBMISSION NO.: S498997
MRID NUMBER: 43750726
TOX CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYMS: Imiprothrin

CITATION: Nakanishi T. 1992. Skin Sensitization Test of S-41311 in Guinea Pigs (Maximization Method). Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd., Osaka, Japan. Laboratory Report No. SGT-20-0018. March 11, 1992. MRID 43750726. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan.

EXECUTIVE SUMMARY: In a Magnusson and Kligman test (MRID # 43750726), a group of 20 male Hartley guinea pigs received intradermal injections of 5% and 10% S-41311 in Freund's complete adjuvant (FCA) and distilled water followed by dermal application of 25% S-41311 in corn oil during the induction phase. Two weeks later, a topical challenge dose of 25% S-41311 in corn oil was administered to animals.

The positive control group (5 males) received 0.05% and 0.1% 2,4-dinitrochlorobenzene (DNCB) in FCA and distilled water intradermally and 0.5% DNCB in corn oil dermally during the induction phase. The S41311 and DNCB non-sensitized groups were treated only during the challenge phase.

At 24 hours, very slight erythema was noted in 3 of 20 S-41311 sensitized animals while all positive controls developed moderate to severe erythema. No reactions were noted in non-sensitized groups. **These results indicate that S-41311 is a mild sensitizer in guinea pigs.**

The study is classified as acceptable and satisfies the requirements (81-6) for a dermal sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality and Flagging statements were provided.

I. MATERIALS

A. MATERIALS:

1. Test Material:
Description: Viscous liquid
Lot/Batch #: LO-910802B
Purity: 95.3% a.i.
CAS #: Not available

2. Vehicle and positive control:

Vehicle: Corn oil
Positive control: 2,4-Dinitrochlorobenzene (DNCB)
Lot #: ECQ 4278
Purity: ≥98.5%

3. Test Animals: Species: Hartley guinea pigs
Source: Charles River Company, Ltd., Japan
Age and weight at the start of treatment: 3-4 weeks; Males - 321-414 kg at dosing
Acclimation period: 7 days quarantine period followed by 5 days of acclimation
Diet: GC-4 Diet (Oriental Yeast Company, Ltd., Tokyo) *ad libitum*
Water: Tap water *ad libitum*
Housing: 5 males per aluminum cage
Environmental Conditions: Temperature: 24±2°C
Humidity: 55±15%
Air Changes: ≥10/hour
Photoperiod: 12 hours light

B. STUDY DESIGN and METHODS:

1. In life dates - start: November 26, 1991
end: December 20, 1991

2. Animal assignment and treatment -

The study was conducted using the maximization test of Magnusson and Kligman method.

Preliminary Test

In a preliminary test, guinea pigs (number unspecified) received intradermal injections (0.05 mL/site) of the test substance in corn oil at concentrations of 0.1%, 0.5%, 1%, and 5%. No dermal reactions were noted. When 25% solution was applied using a patch, no erythema or edema were observed. A 50% solution was too viscous to be applied using a patch. Based on these results, during

the main study, the 5% and 25% test concentrations were selected for intradermal injection and epidermal application, respectively; 25% test concentration was selected for the challenge dose.

Main study

The animals were assigned to four groups as summarized below.

Groups (No. of animals)	Intradermal induction	Percutaneous induction	Challenge application
S-41311 Sensitized (20)	•FCA[a] + distilled water •5% S-41311 in corn oil •10% S-41311 in FCA + distilled water	25% S-41311 in corn oil	25% S-41311 in corn oil
S-41311 non-sensitized (20)	•FCA + distilled water •Corn oil •FCA + distilled water	Corn oil	25% S-41311 in corn oil
DNCB sensitized (5)	•FCA + distilled water •0.05% DNCB in corn oil •0.1% DNCB in FCA + distilled water	0.5% DNCB in corn oil	•0.5% DNCB in corn oil
DNCB non-sensitized (5)	•FCA + distilled water •Corn oil •FCA + distilled water	Corn oil	•0.5% DNCB in corn oil

[a] Freund's complete adjuvant

Induction Phase

During intradermal induction, six injections in three groups of two per animal, were administered in the clipped area in the suprascapular region (injection site: 2 x 4 cm) as follows:

S-41311 sensitized group received two injections (one on each side) each of 0.05 ml Freund's adjuvant/saline in the upper row; 2 injections each of 0.05 ml of 5% S-41311

in corn oil (0.05% DNCB in DNCB sensitized group) in the middle row; and 2 injections each of 0.05 ml Freund's adjuvant with S-41311 diluted to 10% emulsion with corn oil (0.1% DNCB in FCA and distilled water to DNCB sensitized group) in the lower row.

S-41311 and DNCB non-sensitized animals received similar injections with formulating agent but without the test substance. Skin reactions were recorded 24 hours after beginning of intradermal phase.

During epidermal application (6 days after intradermal injections), 0.2 g of 10% sodium lauryl sulfate in petroleum was applied over the injection sites. A day later, 2 x 4 cm lint patch impregnated with 0.4 ml of 25% S-41311 in corn oil was placed over the test site (0.4 ml of 0.5% DNCB in corn oil in DNCB sensitized group). The patch was secured by dressing for 48 hours. The non-sensitized groups (S-41311 and DNCB), received similar treatment but without S-41311 or DNCB, respectively. Evaluations for signs of dermal irritation were made at 24 and 48 hours post application.

Challenge Phase

Two weeks following the epidermal application, a 2 x 2 cm patch of lint patch impregnated with 0.2 ml of 25% S-41311 in corn oil was applied. The patch was secured in place with surgical tapes for 24 hours in S-41311 sensitized and non-sensitized groups. The DNCB sensitized and non-sensitized groups received 0.2 ml of 0.5% DNCB in corn oil. After a twenty-four hour exposure period, the application sites were examined at 24 and 48 hours post-dosing using the standard shown below.

Score	Basis of judgement
0	No reaction
1	Slight reaction (with no clear boundary)
2	Moderate reaction (with clear boundary)
3	Severe reaction

Based on percentage of animals sensitized at the 24-hour reading, the test article was assigned to one of the five grades of allergenic potency ranging from weak (Grade I) to extreme (Grade V) according to the standard by Magnusson and Kligman shown below.

Sensitization rate (%)	Grade	Classification
0 - 8	I	Weak
9 - 28	II	Mild
29 - 64	III	Moderate
65 - 80	IV	Strong
81 - 100	V	Extreme

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration -

No skin reactions were observed in S-41311 sensitized and non-sensitized animals.

B. Challenge reactions and duration - Twenty-four and 48 hours after the challenge application, very slight erythema (severity grade: 1) was noted in 3 of 20 (15%) S-41311 sensitized animals which persisted in one animal at the 48-hour observation period. No skin reactions were noted in S-41311 non-sensitized animals.

C. Positive control - For the positive controls, all the DCNB sensitized animals showed moderate to severe erythema and slight to severe edema (severity grade: 2-3) at 24 and 48 hours indicating strong sensitization potential. No skin reactions were noted in DNCB non-sensitized animals.

E. Deficiencies - The sensitization potential of S-41311 was tested only in male guinea pigs. However, this deficiency does not negatively impact upon the results of the study.

S-41311 Dermal Sensitization Study (81-6)

Reviewed by: Sanjivani B.Diwan, Ph.D. Sanjivani Diwan, Date: 6/5/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y M Ioannou, Date: 6/6/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization - Guinea Pig
OPPTS 8700.2600 [§81-6]

DP BARCODE: D222183
P. C. CODE: 004006
SUBMISSION NO.: S498997
MRID NUMBER: 43750727
TOX CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYMS: Imiprothrin

CITATION: Nakanishi T. 1992. Skin Sensitization Test of S-41311 in Guinea Pigs (Buehler Method). Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd., Osaka, Japan. Laboratory Report No. SGT-20-0019. March 11, 1992. MRID 43750727. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID # 43750727) using the Buehler method, a group of ten male Hartley albino guinea pigs received three topical induction doses of 25% S-41311 in corn oil at weekly intervals. Two weeks later during the challenge phase, the animal received topical application of 25% S-41311 in corn oil.

The positive control group (5 males) received 1% 1,2-dinitrochlorobenzene (DNCB) in acetone during induction phase and 0.5% DNCB during the challenge phase. The S-41311 and DNCB non-sensitized groups were treated during the challenge phase only.

No skin reactions were observed in the S-41311 sensitized and non-sensitized groups. The DNCB sensitized group showed slight to moderate sensitization while no skin reactions were noted in DNCB non-sensitized group. **The results of this study indicate that S-41311 is a non-sensitizer in guinea pigs.**

The study is classified as acceptable and satisfies the requirements (81-6) for a dermal sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality and Flagging statements were provided.

I. MATERIALS

A. MATERIALS:

1. Test Material:
Description: Liquid
Lot/Batch #: LO-910802B
Purity: 95.3% a.i.
CAS #: Not available

2. Vehicle and positive control:

Vehicle: Corn oil
Positive control: 2,4-Dinitrochlorobenzene (DNCB)
Lot #: ECQ 4278
Purity: ≥98.5%

3. Test Animals: Species: Hartley guinea pigs
Source: Charles River Company, Ltd., Japan
Age and weight at the start of treatment: 3 weeks;
Males - 321-420 g at dosing
Acclimation period: 7 days quarantine period followed by 6 days of acclimation
Diet: GC-4 Diet (Oriental Yeast Company, Ltd., Tokyo) *ad libitum*
Water: Tap water *ad libitum*
Housing: 5 males per aluminum cage
Environmental Conditions: Temperature: 24 ± 2°C
Humidity: 55 ± 15%
Air Changes: ≥10/hour
Photoperiod: 12 hours light

B. STUDY DESIGN and METHODS:

1. In life dates - start: January 22, 1992
end: February 21, 1992

2. Animal assignment and treatment -

The study was conducted using the Buehler method.

Preliminary Test

In a dose range-finding study, no irritation was observed in guinea pigs (number unspecified) receiving dermal application of 25% S-41311 in corn oil. The undiluted S-41311 (50% formulation) was too viscous to

be applied using a patch. Based on these findings, 25% S-41311 concentration was chosen for the induction and the challenge phases for the test group and negative control groups during the main study.

Main Study

The animals were assigned to four groups as summarized below.

Group	Number of Animals	Induction Concentration	Challenge Concentration
S-41311 sensitized group	10	25% S-41311 in corn oil	25% S-41311 in corn oil
S-41311 non-sensitized group	10	--	25% S-41311 in corn oil
DNCB sensitized group(Positive control)	5	1% DNCB in acetone	0.5% DNCB in acetone
DNCB non-sensitized group	5	--	0.5% DNCB

Induction Phase

A total of three weekly induction doses were applied using the procedure described below. For the test material, all three induction applications were made to the clipped area in the flank region. A lint patch (1.5 x 1.5 inch) impregnated with 0.5 ml of S-41311 or DNCB was applied to the flanked skin. The patch was secured in place with a surgical tape. After six hours of exposure, evaluations for signs of skin irritation (erythema and edema) were made, at 24 and 48 hours post application, using the following standard:

Grade	Reaction to Treatment
0	no reaction
1	slight reaction (with no clear boundary
2	moderate reaction with clear boundary
3	Severe reaction

Both the S-41311 and DNCB non-sensitized groups received similar treatment but without the test material or DNCB.

Challenge Phase

Two weeks following the last induction dose, the challenge doses of 25% S-41311 in corn oil were applied to the test site of the S-41311 sensitized and non-sensitized animals using the same procedure as in the induction phase. DNCB sensitized and non-sensitized groups received 0.5 ml of 0.5% DNCB in acetone in the same manner. The application sites were examined at 24 and 48 hours post-dosing for the severity of skin reaction.

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration -

No skin reactions were observed in the S-41311 sensitized and non-sensitized animals.

B. Challenge reactions and duration - Twenty-four and 48 hours after the challenge application, no skin reactions were noted in the S-41311 sensitized and non-sensitized animals.

C. Positive control - All DNCB sensitized animals exhibited moderate erythema and slight to moderate swelling after 24 hours, and slight to moderate erythema and slight swelling after 48 hours (severity grade: ≥ 1). No skin reactions were observed in DNCB non-sensitized animals. All animals gained weight during the course of the study.

E. Deficiencies - The sensitization potential of S-41311 was tested in male guinea pigs only. However, this deficiency does not negatively impact upon the results of the study.

012119

IMIPROTHRIN

SALMONELLA/E. COLI (84-2)

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED (7509C)

Signature: Nancy E. McCarroll
Date: 3-28-96

Secondary Reviewer: Sanjivani B. Diwan, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)

Signature: Sanjivani Diwan
Date: 3-28-96

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium/Escherichia coli mammalian microsome mutagenicity assay; OPPTS 870.5100/5265 [§84-2]

DP BARCODE: D222183 SUBMISSION NO.: S498997

PC CODE: 004006 TOX. CHEM. NO.: MRID NO: 43750734

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYM(S): S-4056F; [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate

CITATION: Kogiso, S. (1992). Reverse mutation test of S-41311 in bacteria; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0023; Study Completion Date: May 6, 1992. (Unpublished) MRID NUMBER: 43750734

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

EXECUTIVE SUMMARY: In two independently performed preincubation microbial reverse gene mutation assays (MRID No. 43750734), Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and Escherichia coli strain WP2 uvrA were exposed to 156-5000 μg/plate S-41311 (95.3%) in both the presence and absence of S9 activation. The S9 fraction was derived from Aroclor 1254 induced Sprague Dawley rat livers and S-41311 was delivered to the test system in dimethyl sulfoxide.

Compound precipitation was seen at 5000 μg/plate -S9. All strains responded in the expected manner to the appropriate positive control. There was, however, no evidence that the test material was cytotoxic or mutagenic at any dose with or without S9 activation.

This study is classified as Acceptable and satisfies the guideline requirements for a bacterial gene mutation assay (84-2).

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

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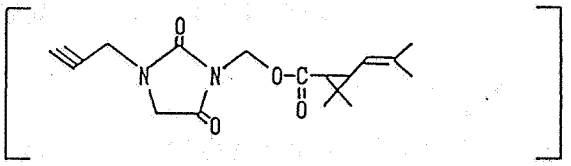
I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311

Description: Not provided
Lot/batch number: LO-910802B
Purity: 95.3%
Receipt date: Not reported
Stability: Not listed
CAS number: Not available
Structure:



Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Neither the storage conditions nor the frequency of test material dosing solution preparation were reported. Analytical determinations to verify actual concentrations were not performed.

2. Control Materials:

Negative: None

Solvent/final concentration: DMSO/not reported but presumed to be 100 µL/plate

Positive:

Nonactivation:

Sodium azide	0.5	µg/plate TA1535
2-Nitrofluorene	2	µg/plate TA1538
9-Aminoacridine	80	µg/plate TA1537
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2)	0.1	µg/plate TA98
	0.01	µg/plate TA100
N-Ethyl-N'-nitro-N-nitroso-guanidine	2	µg/plate WP2 uvrA

Activation:

2-Aminoanthracene	2	µg/plate TA1535
	10	µg/plate WP2 uvrA
Benzo[a]pyrene	5	µg/plate TA1537, TA1538, TA98 and TA100

3. Activation: S9 derived from 8- to 10-week old (sex unspecified) Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other	_____ other		

The rat liver S9 homogenate (Lot No. 33503) was purchased from Organon Teknika Co., West Chester, PA. The S9 mix contained the following components:

Component	Amount/mL
200 mM Na-phosphate buffer (pH 7.4)	0.5 mL
Glucose-6-phosphate	1.7 mg
NADPH	3.62 mg
NADH	3.05 mg
20 mM $MgCl_2$/82.5 mM KCl	0.4 mL
S9	0.1 mL

4. Test Organism Used: S. typhimurium strains

_____ TA97	x TA98	x TA100	_____ TA102	_____ TA104
x TA1535	x TA1537	x TA1538		

list any others: E. coli WP2 uvrA

Test organisms were properly maintained? Yes.
Checked for appropriate genetic markers (rfa mutation, R factor)? Yes.

5. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Six doses (15, 50, 150, 500, 1500 or 5000 µg/plate +/-S9) were assayed using all strains. Single plates were prepared per dose, per strain, per condition; positive controls were included.

(b) Mutation assays:

Trial 1: Six doses (156, 313, 625, 1250, 2500 or 5000 µg/plate +/-S9) were assayed using all strains. Triplicate plates were prepared per dose, per strain, per condition.

Trial 2: As above for Trial 1.

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B. TEST PERFORMANCE

1. Type of Salmonella Assay:

___ Standard plate test
_x_ Pre-incubation (20) minutes
___ "Prival" modification
___ Spot test
___ Other (describe)

2. Preliminary Cytotoxicity Test/Mutation Assays: Similar procedures were used for the preliminary cytotoxicity test and the two mutation assays with the exception that in the cytotoxicity assay, only single plates per dose, per condition were prepared.

The following were added to sterile tubes:

- The selected test doses, solvent, or positive controls, in 0.1-mL volumes.
- The appropriate tester strain (12-hour broth culture containing $\approx 10^9$ cells/mL) in 0.1 mL volumes
- 0.5 mL of 100 mM phosphate buffer (nonactivated test) or 0.5 mL of the S9-mix (S9-activated test).

Reaction mixtures were preincubated with shaking at 37°C for 20 minutes and mixed with 2 mL of top agar supplemented with 0.5 mM L-histidine, 0.5 mM D-biotin, and 0.5 mM L-tryptophan. The contents of each tube were overlaid onto plates of minimal glucose agar. Plates were incubated for 65 hours at 37°C. Following incubation, the number of revertant colonies was counted and average values were determined.

3. Evaluation Criteria: The test material was considered positive if it caused a ≥2-fold increase in the spontaneous reversion count of any strain and the response was dose related.

C. REPORTED RESULTS

1. Preliminary Cytotoxicity Assay: Six doses ranging from 15 to 5000 µg/plate +/-S9 were evaluated in the preliminary cytotoxicity test using all strains. The nonactivated high dose was insoluble. Revertant colony counts for all strains were generally comparable to the respective solvent control results with or without S9 activation. Based on these results, concentrations selected for the first mutation assay ranged from 156 to 5000 µg/plate +/-S9.

2. Mutation Assays: Results from both trials of the mutation assay were in good agreement with the preliminary data and indicated that compound precipitation occurred only at the highest nonactivated dose. There was also no evidence of a cytotoxic or mutagenic response at any nonactivated or S9-activated dose in any strain. By contrast to the uniformly negative

findings with the test material, all strains responded in the expected manner to the corresponding nonactivated or S9-activated positive control. Representative data from both trials are presented in Tables 1 and 2.

Based on the overall findings, the study author concluded that S-41311 was not mutagenic in this microbial reverse mutation assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study was properly conducted and that the test material failed to induce a mutagenic response when tested up to the recommended high concentration for bacterial gene mutation assays (5000 μg/plate). Additionally, the sensitivity of the test system to detect genotoxicity was adequately demonstrated by the results obtained with the appropriate nonactivated and S9-activated positive controls. Based on the overall results, we conclude that the data provide acceptable evidence that S-41311 is not a mutagen for bacteria.

E. STUDY DEFICIENCIES: NONE

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TABLE 1: Representative Results of the Initial Salmonella typhimurium/Escherichia coli Preincubation Mutagenicity Assay with S-41311

			Revertants per Plate of Bacterial Tester Strains[a]					
			S.typhimurium					E. coli
Substance	Dose/Plate	S9-Activation	TA1535	TA1537	TA1538	TA98	TA100	WP2 uvrA
Solvent Control								
Dimethyl sulfoxide	100 µL	-	11	9	10	20	77	25
	100 µL	+	10	27	28	37	93	40
Positive Controls[b]								
Sodium azide	0.5 µg	-	286	--	--	--	--	--
2-NF	2 µg	-	--	--	509	--	--	--
9-AA	80 µg	-	--	491	--	--	--	--
AF-2	0.1 µg	-	--	--	--	223	--	--
	0.01 µg	-	--	--	--	--	333	--
ENNG	2 µg	-	--	--	--	--	--	468
2-AA	2 µg	+	182	--	--	--	--	--
	10 µg	+	--	--	--	--	--	651
B(a)P	5 µg	+	--	182	233	355	560	--
Test Material								
S-41311	2500 µg	-	6	8	17	23	69	16
	5000 µg[c]	-	8	4	11	29	91	13
	2500 µg	+	10	32	40	55	103	31
	5000 µg	+	9	18	35	56	96	34

[a]Average values from triplicate plates
[b]Abbreviations:

2-NF = 2-Nitrofluorene
9-AA = 9-Aminoacridine
AF-2 = 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
ENNG = N-Ethyl-N'-nitro-N-nitrosoguanidine
2-AA = 2-Aminoanthracene
B(a)P = Benzo(a)pyrene

[c]Compound precipitation was reported at this dose. Data for lower concentrations (156, 313, 625 or 1250 µg/plate +/-S9) did not suggest a mutagenic response.

NOTE: Data were extracted from the study report, Tables 2-1 and 2-2; pp. 20 and 21.

TABLE 2 Representative Results of the Repeat Salmonella typhimurium/Escherichia coli Preincubation Mutagenicity Assay with S-41311

			Revertants per Plate of Bacterial Tester Strains[a]					
			S.typhimurium					E. coli
Substance	Dose/Plate	S9-Activation	TA1535	TA1537	TA1538	TA98	TA100	WP2 uvrA
Solvent Control								
Dimethyl sulfoxide	100 µL	-	11	11	13	24	87	22
	100 µL	+	10	22	37	49	91	31
Positive Controls[b]								
Sodium azide	0.5 µg	-	296	--	--	--	--	--
2-NF	2 µg	-	--	--	619	--	--	--
9-AA	80 µg	-	--	804	--	--	--	--
AF-2	0.1 µg	-	--	--	--	295	--	--
	0.01 µg	-	--	--	--	--	357	--
ENNG	2 µg	-	--	--	--	--	--	493
2-AA	2 µg	+	231	--	--	--	--	--
	10 µg	+	--	--	--	--	--	649
B(a)P	5 µg	+	--	126	106	195	467	--
Test Material								
S-41311	2500 µg	-	8	8	11	21	97	20
	5000 µg[c]	-	11	6	15	31	94	21
	2500 µg	+	11	28	30	52	101	33
	5000 µg	+	11	19	38	49	97	35

[a]Average values from triplicate plates
[b]Abbreviations:

2-NF = 2-Nitrofluorene
9-AA = 9-Aminoacridine
AF-2 = 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
ENNG = N-Ethyl-N'-nitro-N-nitrosoguanidine
2-AA = 2-Aminoanthracene
B(a)P = Benzo(a)pyrene

[c]Compound precipitation was reported at this dose. Data for lower concentrations (156, 313, 625 or 1250 µg/plate +/-S9) did not suggest a mutagenic response.

NOTE: Data were extracted from the study report, Tables 3-1 and 3-2; pp. 22 and 23.

012119

IMIPROTHRIN

MAMMALIAN CELLS IN CULTURE CYTOGENETICS (84-2)

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED (7509C)

Signature: Nancy E. McCarroll
Date: 3-28-96

Secondary Reviewer: Sanjivani B. Diwan, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)

Signature: Sanjivani Diwan
Date: 3-28-96

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mammalian cells in culture cytogenetic assay in Chinese hamster lung cells; OPPTS 870.5375 [§84-2]

DP BARCODE: D222183 SUBMISSION NO.: S498997

PC CODE: 004006 TOX. CHEM. NO.: MRID NO: 43750735

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYM(S): S-4056F; [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate

CITATION: Hara, M. (1992). In vitro chromosomal aberration test of S-41311 in Chinese hamster lung cells (CHL/IU); Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0024; Study Completion Date: April 9, 1992. (Unpublished) MRID NUMBER: 43750735

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

EXECUTIVE SUMMARY: In a mammalian cell cytogenetic assay (MRID No. 43750735), Chinese hamster lung cells (CHL/IU) were exposed continuously to S-41311 (95.3%) doses of 50-200 μg/mL in the absence of metabolic activation for 24 or 48 hours. Cells were also exposed to nonactivated doses of 75-300 μg/mL or S9-activated doses of 25-100 μg/mL for 6 hours and harvested following an 18-hour recovery period. The S9 homogenate was derived from Aroclor 1254-induced rat livers and the test material was delivered to the test system in dimethyl sulfoxide.

Severe cytotoxicity was seen at 200 μg/mL -S9 (24 and 48 hours of treatment) and at 300 μg/mL -S9 (6 hours of treatment). The positive controls induced the expected genotoxic responses. In the absence of S9 activation, there was no evidence of clastogenicity. However, dose-related increases in the yield of cells with structural damage were seen in the presence of S9 activation. The incidence of cells with abnormal chromosome morphology was 2.5, 7.5 or 34.0% at 50, 75 or 100 μg/mL, respectively, as compared to an incidence rate of 1.5% in the solvent control group. Structural damage in the treatment groups was primarily manifested as chromatid breaks and exchanges. The incidence of polyploid cells was also increased (11 or 31.5%) at 50 or 75 μg/mL, respectively, but not at the high dose. Overall the data provide clear evidence that S9-activated S-41311 is clastogenic in this in vitro test system.

This study is classified as Acceptable and satisfies the guideline requirement for a cytogenetic assay (§84-2).

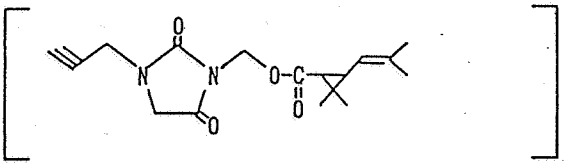
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311

Description: Not provided
Lot/batch number: LO-910802B
Purity: 95.3%
Receipt date: Not reported
Stability: Not listed
CAS number: Not available
Structure:



Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Storage conditions for the test material were not reported. Dosing solution were prepared immediately prior to use. Analytical determinations were not performed to verify actual concentrations.

2. Control Materials:

Negative: None

Solvent/final concentration: DMSO/0.5%

Positive:

Nonactivation: Mitomycin C (MMC) was prepared in physiological saline to yield a final concentration of 0.03 μg/mL.

Activation: Cyclophosphamide (CP) was prepared in physiological saline to yield a final concentration of 15 μg/mL.

3. Activation: S9 derived from Sprague-Dawley (sex and age not specified)

x Aroclor 1254	x induced	x rat	x liver
_____ phenobarbital	_____ noninduced	_____ mouse	_____ lung
_____ none		_____ hamster	_____ other
_____ other	_____ other		

The rat liver S9 homogenate (Lot No. 2013) had a protein concentration of 33.6 mg/mL and was purchased from Organon Teknika Co., West Chester, PA. The S9 mix contained the following components:

Component	Amount/10 mL
HEPES buffer (20 mM; pH 7.2)	2.0 mL
Glucose-6-phosphate	50 µmol
NADPH	40 µmol
KCl (330 mM)	1.0 mL
$MgCl_2$ (50 mM)	1.0 mL
H_2O (distilled)	3.0 mL
S9 homogenate	3.0 mL (30%)

Note: Final concentration of the S9 in the treatment medium [Eagle's minimal essential medium (MEM)] was 5%.

4. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Nine doses (3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500 and 1000 µg/mL +/- S9) were evaluated using duplicate cultures per dose, per condition, per harvest time. Cell counts were determined after 24 or 48 hours exposure to the nonactivated test material or after 6 hours of exposure to either the nonactivated or S9-activated test material followed by an 18-hour recovery period.

(b) Cytogenetic assay: Duplicate cultures per dose, per condition, per exposure duration were evaluated as follows:

Nonactivated conditions:

- 50, 100, 150 and 200 µg/mL (cell harvest following either 24 or 48 hours of continuous treatment).
- 75, 150, 225 and 300 µg/mL (cell harvest following 6 hours of treatment and an 18-hour recovery period).

S9-activated conditions:

- 25, 50, 75 and 100 µg/mL (cell harvest following 6 hours of treatment and an 18-hour recovery period).

5. Test Cells: Chinese hamster lung cells (CHL/IU) were obtained from Dainippon Pharmaceutical Co., Ltd., Osaka, Japan. Cells were grown in Eagle's MEM supplemented with 10% calf serum at 37°C in 5% CO_2 for 3 days prior to use.

Properly maintained? Yes.
Cell line or strain periodically checked for mycoplasma contamination? Yes.

Cell line or strain periodically check for karyotype stability? Not reported.

B. TEST PERFORMANCE:

1. Cell Treatment: Cells were exposed to the test compound, negative, solvent or positive control for:

   6, 24 or 48 hours (nonactivated),
   6 hours (activated)

2. Preliminary Cytotoxicity Assay: Duplicate cultures, seeded at a density of $\approx 1 \times 10^4$ cells/plate, were exposed to nine concentrations of the test material (3.9-1000 µg/mL +/- S9) or the solvent (DMSO). Under nonactivated conditions, cells were exposed to the test material continuously for either 6, 24 or 48 hours. At the end of the 6-hour treatment, cell were washed and recultured in fresh Eagle's MEM and incubated for an additional 18 hours. Cultures exposed to S9-activated test material doses were also treated for 6 hours, washed, refed fresh culture medium and incubated for an additional 18 hours. At the conclusion of exposure and/or recovery, cells were trypsinized and counted.

3. Cytogenetic assay:

   (a) Treatment: Cell treatment was similar to that described above for the preliminary cytotoxicity assay with the exceptions that positive controls were included and colcemid (final concentration 0.1 µg/mL) was added to each culture 1.5 hours prior to cell harvest.

   Metaphase cells were harvested, treated with hypotonic KCl (75 mM), fixed with methanol:acetic acid (3:1), spread onto slides, air-dried, and stained with 3% Giemsa.

   (b) Metaphase analysis: The slides were coded, and at least 200 cells (100 cells/culture) from each treatment, solvent or positive control group were scored for structural chromosomal aberrations. Chromatid and chromosome gaps were counted but not included in the final analysis. The frequency of polyploid cell in 100 metaphase spreads per group was also determined.

4. Statistical methods: No statistical analysis was performed.

5. Evaluation Criteria: The test material was considered positive if the frequency of cells with structural aberrations was ≥10% of the corresponding solvent control value and the response was dose-related or reproducible.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Assay: Doses ranging from 3.9-1000 μg/mL were assayed in both the presence and absence of S9 activation. S-41311 was insoluble at levels ≥250 μg/mL +/-S9. Under all nonactivated test conditions, survival was generally dose and time related. Approximately ≤10% of the cells survived 6, 24 or 48 hours of treatment with the two highest nonactivated concentrations (500 and 1000 μg/mL). Survival at 250 μg/ml -S9 ranged from 32% after 6 hours of treatment and 18 hours of recovery to 2.7% following 48 hours of continuous exposure. At 62.5 or 125 μg/mL -S9, ≈74 or 40%, respectively, of the cells were recovered regardless of the exposure duration. There was no clear evidence of cytotoxicity in the remaining nonactivated treatment groups. Growth rates under S9-activated conditions were also dose dependent and ranged from ≈10% at the high dose (1000 μg/mL) to ≈60% at 62.5 μg/mL. Lower S9-activated levels (≤31.3 μg/mL) were not cytotoxic.

2. Cytogenetic Assays: Based on the findings of the preliminary cytotoxicity assessment, the following doses and exposure times were selected for the cytogenetic assay:

   50, 100, 150 or 200 μg/mL -S9 -- 24 or 48 hours of continuous exposure

   75, 150, 225 or 300 μg/mL -S9 -- 6-hour exposure and 18-hour recovery

   25, 50, 75 or 100 μg/mL +S9 -- 6-hour exposure and 18-hour recovery

   Results were as follows:

   Nonactivated conditions: Summarized results from the prolonged exposure (24 or 48 hours) of CHL cells to the nonactivated test material are shown in Study Report Table 2, p.23 (see Attachment). The high dose (200 μg/mL -S9) was severely cytotoxic at both time intervals and 150 μg/mL was cytotoxic after 48 hours of treatment. No appreciable increase in either structural or numerical chromosomal aberrations was, however, seen at any noncytotoxic dose or treatment time. Cytotoxicity (at 300 μg/mL) but no clastogenicity was also obtained when cells were exposed to nonactivated S-41311 for 6 hours and permitted an 18-hour recovery period (Study Report Table 3, p. 24--see Attachment).

   S9-activated conditions: By contrast to the nonactivated findings, marked increases in the yield of cells with structural chromosome damage were seen in cultures exposed to the S9-activated test material for 6 hours and harvested after an 18-hour recovery period. The clastogenic response was dose related with structural aberration frequencies of 2.5, 7.5 and 34% at 50, 75 and 100 μg/mL, respectively. Structural damage was largely manifested as chromatid breaks and exchanges. There was also an increased incidence of polyploid cells at 50 and 75 μg/mL (11.0 and 31.5%, respectively) but not at the high dose.

Based on the overall results, the study author concluded that S9-activated S-41311 was clastogenic in this cytogenetic assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We agree with the study author's interpretation of the results and conclude that S-41311 at 75 and 100 μg/mL is genotoxic in cultured CHL mammalian cells but only in the presence of exogenous metabolic activation. Under nonactivated conditions, S-41311 was assayed to cytotoxic levels (300 μg/mL -- 6-hour treatment; 200 μg/mL -- 24-hour treatment, or ≥150 μg/mL -- 48-hour treatment) but did not induce a clastogenic effect. In addition, the sensitivity of the test system to detect a clastogenic response was adequately demonstrated by the results obtained with the positive control compounds (MMC and CP). We assess, therefore, that the study provides acceptable evidence that S-41311 is a clastogen in this in vitro mammalian cell line.

E. STUDY DEFICIENCIES: NONE.

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_____ Identity of product impurities.

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_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

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√ FIFRA registration data.

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_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

012119

IMIPROTHRIN

MICRONUCLEUS (84-2)

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED (7509C)

Signature: Nancy E. McCarroll
Date: 3-19-96

Secondary Reviewer: Sanjivani B. Diwan, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)

Signature: Sanjivani Diwan
Date: 3-19-96

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mouse micronucleus assay; OPPTS 870.5395 [§84-2]

DP BARCODE: D222183 SUBMISSION NO.: S498997

PC CODE: 004006 TOX. CHEM. NO.: MRID NO: 43750736

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYM(S): S-4056F; [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate

CITATION: Hara, M. (1992). Micronucleus test of S-41311 in mice; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0041; Study Completion Date: April 28, 1992. (Unpublished) MRID NUMBER: 43750736

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

EXECUTIVE SUMMARY: In a mouse micronucleus assay (MRID No: 43750736), groups of five male and five female CD-1 ICR mice received single intraperitoneal injections of 19, 38 or 75 mg/kg S-41311 (95.3%) prepared in corn oil. Animals were sacrificed at 24, 48 and 72 hours postadministration; bone marrow cells were harvested and examined for the incidence of micronucleated polychromatic erythrocytes (MPEs).

Overt toxicity in the 75-mg/kg dose group included two deaths and tremors, clonic convulsions, prone position, ataxic gait and urinary incontinence. The positive control induced the expected high yield of MPEs in both sexes. There was, however, no evidence that the test material induced a cytotoxic, clastogenic or aneugenic effect at any dose or sacrifice time.

The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for in vivo cytogenetic mutagenicity data.

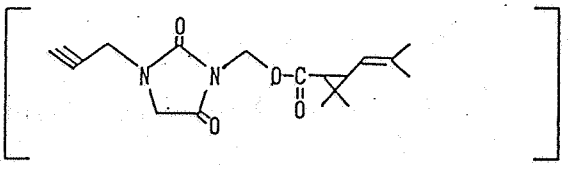
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311

Description: Not provided
Lot/batch number: LO-910802B
Purity: 95.3%
Receipt date: Not reported
Stability: Not listed
CAS number: Not available
Structure:



Vehicle used: Corn oil
Other provided information: The test material was stored in a cool and dry place. Test material dosing solutions were prepared immediately prior to use. Analytical determinations were not performed to verify actual concentrations.

2. Control Materials:

Negative: None

Vehicle/final concentration/route of administration: Corn oil at a dosing volume of 10 mL/kg was administered by intraperitoneal (ip) injection

Positive/final dose(s)/route of administration: Cyclophosphamide was dissolved in physiological saline and administered ip at 40 mg/kg.

3. Test Compound:

Route of administration: Ip

Volume of test substance administered: 10 mL/kg.

Dose levels used:

Preliminary toxicity test: 50, 75, 100 and 150 mg/kg (5 males and 5 females per group)

Micronucleus assay: 19, 38 and 75 mg/kg (5 males and 5 females per group per sacrifice time)

4. Test Animals:

(a) Species: Mouse; Strain: CD-1 ICR; Age (at initiation): 8 weeks; Weight range:

Preliminary toxicity test: 33.5-40.1 g (♂); 22.4-28.4 g (♀)
Micronucleus assay: 33.0-42.4 g (♂); 25.8-33.2 g (♀)
Source: Charles River Japan Inc., Kanagawa, Japan

(b) Number of animals used per dose:

Preliminary toxicity test: 5 ♂ and 5♀ per treatment and vehicle control group

Micronucleus assay: 5 ♂ and 5 ♀ per treatment and vehicle control group per sacrifice.

5 ♂ and 5 ♀ positive control group

Note: An additional group of 10 males and 10 females received the high dose used in the micronucleus assay and were held in reserve in the event of unscheduled deaths in the primary group.

(c) Were test animals properly maintained? Yes.

B. TEST PERFORMANCE

1. Micronucleus Assay:

(a) Treatment and sampling times:

1. Test compound and vehicle control:
Dosing: __x__ once _____ twice (24 hours apart)
_____ other (describe):

Sampling (after last dose): _____ 6 hours _____ 12 hours
__x__ 24 hours __x__ 48 hours __x__ 72 hours

2. Positive control:
Dosing: __x__ once _____ twice (24 hours apart)
_____ other (describe):

Sampling (after last dose):
__x__ 24 hours _____ 48 hours _____ 72 hours

3. Tissues and Cells Examined:

__x__ bone marrow _____ other (list):
Number of polychromatic erythrocytes (PCEs) examined per animal: 1000

Number of normochromatic erythrocytes (NCEs, more mature RBCs) examined per animal: 1000 total erythrocytes.

4. Details of Cell Harvest and Slide Preparation: At 24, 48 and 72 hours after the administration of the test material or the vehicle control, the appropriate groups of animals were sacrificed by cervical dislocation. Animals in the positive control groups were sacrificed 24 hours postexposure. Bone marrow was flushed from the femurs with fetal bovine serum (FBS). Cells were centrifuged, resuspended in residual supernatant and dropped onto slides. Slides were stained with 5% Giemsa and coded prior to scoring for micronuclei in polychromatic erythrocytes (MPEs) and determining the ratio of PCEs to NCEs.

5. Statistical Methods: The incidence of MPEs was analyzed for statistical significance using the method of Kastenbaum and Bowman. PCE:NCE ratios were analyzed using the t-test. Statistical significance was established at $p<0.05$.

6. Evaluation Criteria: The test material results were considered positive if the incidence of MPEs in any group was significantly higher that the concurrent vehicle control group and the response was dose-related and reproducible. The data were also evaluated relative to historical control data (not provided).

C. REPORTED RESULTS:

1. Preliminary Range-finding Test: Groups of 5 male and 5 female mice received single ip injections of 50, 75, 100 or 150 mg/kg S-41311. Animals were observed for clinical signs and mortality for 4 days postdosing; body weights were recorded on study days 0-4. Deaths occurred within 24 hours of treatment as follows: one male and one female at 100 mg/kg and 5/5 males and 3/5 females at 150 mg/kg. Clinical signs noted in the high-dose group included: tremors, clonic convulsions, prone position, ataxic gait and ptosis. The majority of these signs plus urinary incontinence were observed in the animals that succumbed to treatment with 100 mg/kg. Tremors (50 and 75 mg/kg), clonic convulsions and prone position (75 mg/kg) were recorded for the lower treatment groups. Exposure to S-41311 had no apparent effect on body weight. Based on these data, 75 mg/kg was estimated to be the approximate maximum tolerated dose (MTD). Accordingly, doses selected for the micronucleus assay were 19, 38 and 75 mg/kg.

2. Micronucleus Assay:

(a) Animal observations: One male and one female died in the 75-mg/kg dose group; no unscheduled deaths were reported for the mid- and low-dose groups. Clinical signs similar to those observed in the preliminary toxicity test (i.e., tremors, clonic convulsions, prone position, ataxic gait and urinary incontinence) were noted in the animals exposed to the high dose. Toxic effects were either limited or absent in the 19- and 38-mg/kg test groups.

(b) Bone marrow analysis: Summarized results from the micronucleus assay conducted in male and female mice exposed to S-41311 are presented in Study Report Tables 3 and 4, pp. 22 and 23, respectively. As the data indicate, 19, 38 or 75 mg/kg S-41311 administered by i.p. injection was neither cytotoxic nor genotoxic to bone marrow cells harvested 24, 48 or 72 hours postexposure. By contrast, the positive control (40 mg/kg CP) induced the expected significant ($p<0.01$) yield of MPCEs in both sexes.

Based on the overall findings, the study author concluded that S-41311 did not induced micronuclei in the bone marrow cells of mice under the given test conditions.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We agree with the study author's conclusion that S-41311 was neither clastogenic nor aneugenic in this mouse micronucleus assay. The clear demonstration of compound toxicity, particularly at the high dose (75 mg/kg) indicates that a adequate range of treatment levels were evaluated. Similarly, the response induced by the positive control (40 mg/kg CP) provides confidence that an adequate level of assay sensitivity was achieved. Based on the above considerations, we assess that the data support the conclusion that S-41311 was negative in this in vivo test system.

E. STUDY DEFICIENCIES: NONE.

Information denied

Page _____ is not included in this copy.

Pages 62 through 63 are not included in this copy.

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012119

IMIPROTHRIN

IN VIVO/IN VITRO UDS (84-2)

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED (7509C)

Signature: Nancy E. McCarroll
Date: 3/19/96

Secondary Reviewer: Sanjivani B. Diwan, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)

Signature: Sanjivani B. Diwan
Date: 3/19/96

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: In vivo/in vitro unscheduled DNA synthesis assay in primary rat hepatocytes following in vivo dosage; OPPTS 870.5550 [§84-2]

DP BARCODE: D222183 SUBMISSION NO.: S498997

PC CODE: 004006 TOX. CHEM. NO.: MRID NO: 43750737

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYM(S): S-4056F; [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate

CITATION: Hara, M. (1992). In vivo/in vitro unscheduled DNA synthesis (UDS) test of S-41311 in rat hepatocytes; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0045; Study Completion Date: July 9,1992. (Unpublished) MRID NUMBER: 43750737

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

EXECUTIVE SUMMARY: In an in vivo/in vitro unscheduled DNA synthesis (UDS) study (MRID No. 43750737), groups of three male rats were administered a single oral gavage dose of 1000 mg/kg S-41311 (93.5%) prepared in corn oil and hepatocytes were harvested 3, 12 or 24 hours postdosing (Phase I). For Phase II, groups of three male rats were similarly dosed with 250, 500 or 1000 mg/kg and hepatocytes were collected 3 hours after exposure. Recovered hepatocytes in both phases of testing were scored for UDS.

Signs of toxicity noted in the high-dose rats included one death, tremors and decreased spontaneous activity. The latter two signs were also seen at 500 mg/kg. The results obtained with the positive control confirmed the sensitivity of the test system to detect UDS. **There was no evidence that the test material induced either a cytotoxic or genotoxic response at any dose or sacrifice time.** The study report is, however, incomplete because primary data (i.e., gross nuclear grain counts and cytoplasmic grain counts) were not provided.

The study is currently classified as Unacceptable and does not satisfy the requirements for FIFRA Test Guideline 84-2 for UDS mutagenicity data. It can, however, be upgraded if the missing information is submitted and deemed acceptable.

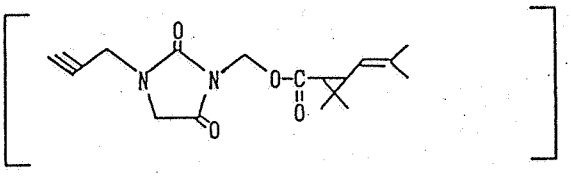
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311

Description: Not provided
Lot/batch number: LO-910802B
Purity: 95.3%
Receipt date: Not reported
Stability: Not listed
CAS number: Not available
Structure:



Vehicle used: Corn oil
Other provided information: Storage conditions for the test material were not reported. Dosing solutions were prepared immediately prior to use. Analytical determinations were not performed to verify actual concentrations.

2. Control Substances:

Vehicle control/concentration/route of administration: Corn oil was administered by oral gavage at a dosing volume of 10 mL/kg.

Positive controls/concentration/route of administration: 2-Acetylaminofluorene (2-AAF) was prepared in corn oil and administered by oral gavage at a final dose of 50 mg/kg (12-hour sacrifice).

3. Medium: WME: Williams' Medium E ; WME+: Williams' Medium E supplemented 10% fetal bovine serum.

4. Test Compound:

Route of administration: Once by oral gavage (dosing volume = 10 mL/kg).

Dose levels:

Phase I: 1000 mg/kg
Phase II: 250, 500 and 1000 mg/kg

Note: The rat oral maximum tolerated dose (MTD) was reported to be ≈1000 mg/kg[1].

5. Test Animals:

(a) Species: Rat; Strain: Sprague-Dawley; Age (at dosing): 6-7 weeks; Sex: Males; Weight range (at dosing): 202-279 g; Source: Charles River Japan, Inc., Kanagawa, Japan

(b) Number of animals/dose:

Phase I: 3 males/treatment group per sacrifice time
3 males/vehicle or positive control group

Phase II: 3 males/test material, vehicle or positive control group

Note: The report indicated that a "few supplemental animals were provided for each group" in the event of unscheduled deaths in the primary groups. No further details were reported.

(c) Properly maintained? Yes.

B. TEST PERFORMANCE

1. UDS Assay:

(a) Treatment and sampling times:

Phase I:

1. Test compound:
Dosing: x once _____ twice (24 hours apart)
_____ other (describe):
Sampling (after last dose): x 3 hours x 12 hours
x 24 hours

2. Vehicle and positive control:
Dosing: x once _____ twice (24 hours apart)
_____ other (describe):
Sampling (after last dose):
___ 3 hours x 12 hours _____ 24 hours

[1]Misaki, Y, Ito, S, Seki, T, Kawasaki, H and Kato, T (1992). Single dose oral toxicity test of S-41311 in rats; Sumitomo Chem. Co.,Ltd.; Technical report, Study No. 2531.

Phase II:

1. Test compound and vehicle
   Dosing: __x__ once _____ twice (24 hours apart)
   _____ other (describe):
   Sampling (after last dose): __x__ 3 hours ____ 12 hours
   ____ 24 hours

2. Positive control:
   Dosing: __x__ once _____ twice (24 hours apart)
   _____ other (describe):
   Sampling (after last dose):
   ___ 3 hours __x__ 12 hours _____ 24 hours

(b) Perfusion techniques/hepatocyte harvest: At 3, 12 or 24 hours postdosing, animals in the appropriate test material groups were anesthetized with Nembutal. Animals in the vehicle and positive control groups were prepared for liver perfusion 3 or 12 hours postdosing. Livers were perfused with a buffer solution and a calcium/collagenase solution. Livers were removed and minced in WME+; suspensions were filtered and hepatocytes were collected by centrifugation. Separated hepatocytes were washed with WME+, centrifuged, resuspended in WEM+ and adjusted to 2.5×10^5 viable cells/mL. Viability was assessed by trypan blue exclusion.

(c) Hepatocyte treatment: Prepared hepatocytes in 2-ml volumes were plated onto coverslips placed in 6-well culture dishes. Four coverslips were made per suspension. Cultures were allowed to attach at 37°C with 5% CO_2 for ≈90 minutes. Unattached cells were removed. Viable cells were incubated in WME containing ^{3}H-thymidine (370 kBq/mL) for 4 hours, washed and reincubated for an additional 16 hours in WME with unlabeled thymidine (0.25 mM).

(d) Slide preparation: Hepatocytes attached to coverslips were washed, treated with 1% sodium citrate, fixed in acetic acid:ethanol (1:3), washed, dried and mounted.

(e) Preparation of autoradiographies/grain development: At least two of four slides per animal were coated with NTB-2 photographic emulsion, exposed at 4°C in the dark for 1 week, developed in Hi Rendol developer, immersed in 2% acetic acid, fixed with Hi Renfix, and stained with Meyer's hematoxylin and eosin Y. All slides were coded prior to analysis.

(d) Grain counting: The grains of at least 100 morphologically normal cells (50/slide/animal) were counted using an image processing system that measures silver grains in an area mode. Areas of silver grains in either the nuclei or nuclear-sized areas of adjacent cytoplasm (cytoplasmic grain count) were converted to grains using least squares as shown below:

Phase I: Number of grains = Area (of each grain) x 0.0329 + 0.2735

Phase II: Number of grains = Area (of each grain) x 0.0269 + 1.5055

Net nuclear grains (NG) were determined by subtracting the cytoplasmic grain count from the nuclear grain count of each cell. The percentage of cells in repair (i.e., cells having ≥5 NG) was also calculated.

(f) Statistical methods: The data were not evaluated for statistical significance.

2. Evaluation Criteria:

(a) Assay validity: The assay was considered acceptable if: (1) the mean NG for the vehicle control group was ≤0 and ≤10% of the cells were in repair and (2) the mean NG for the positive control groups was ≥5 with at least 50% of the cells in repair.

(b) Positive response: The assay was considered positive if the mean NG count for any treatment group was ≥5 with ≥20% of the cells in repair and the effect was dose related.

C. REPORTED RESULTS:

1. Animal Observations: Information provided from the findings of a single oral toxicity test indicated that MTD of S-41311 was ≈1000 mg/kg[2]. Accordingly, 1000 mg/kg with hepatocyte harvests at 3, 12 and 24 hours postdosing was evaluated in Phase I of the UDS assay. Reported clinical signs were tremors and decreased spontaneous activity. In Phase II, doses of 250, 500 or 1000 mg/kg were selected for investigation using a single 3-hour cell harvest. Similar signs of compound toxicity (i.e., tremors and decreased spontaneous activity) were seen at 1000 mg/kg and also at 500 mg/kg. Additionally, ataxic gait was reported for both treatment groups and one of the high-dose rats (1 of 7 including 4 supplemental animals) died within 2.5 hours of S-41311 administration.

2. Hepatocyte analysis: Summarized results from both the time course study (Phase I) and the dose response study (Phase II) are presented in Study Report Tables 1 and 2, pp. 25 and 26, respectively (see Attachment). As shown, S-41311 was neither cytotoxic nor genotoxic to hepatocytes harvested 3, 12 or 24 hours postexposure to doses as high as 1000 mg/kg. By contrast, the positive control (50 mg/kg 2-AAF) induced marked increases in NG and the percentage of cells in repair in both phases of the assay.

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[2]Misaki, Y, Ito, S, Seki, T, Kawasaki, H and Kato, T (1992). Single dose oral toxicity test of S-41311 in rats; Sumitomo Chem. Co.,Ltd.; Technical report, Study No. 2531.

The study author concluded, therefore, that S-41311 was not genotoxic in this whole animal UDS assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that S-41311 was assayed to levels (500 and 1000 mg/kg) that clearly demonstrated the MTD but failed to induce either a cytotoxic or genotoxic response in the hepatocytes of male rats harvested 3, 12 or 24 hours posttreatment with 1000 mg/kg or 3 hours after exposure to 250 or 500 mg/kg. Results with the positive control (2-AAF at 50 mg/kg) indicated that the assay was sufficiently sensitive to detect genotoxicity. However, since only summarized NG count data were provided, we are unable to independent verify the study findings. We conclude, therefore, that the report as presented is incomplete and the study is classified as **Unacceptable**. The study can be upgraded if the missing information (primary data for gross nuclear grain counts and cytoplasmic grain counts) is submitted and deemed acceptable.

E. STUDY DEFICIENCIES : See above regarding missing primary data.

Incomplete Material Reviewed

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IMIPROTHRIN

MAMMALIAN CELLS IN CULTURE GENE MUTATION (84-2)

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED (7509C)

Signature: Nancy E. McCarroll
Date: 3/20/96

Secondary Reviewer: Sanjivani B. Diwan, Ph.D.
Review Section I,
Toxicology Branch II/HED (7509C)

Signature: Sanjivani B. Diwan
Date: 3/20/96

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mammalian cells in culture gene mutation in Chinese hamster lung fibroblasts (V79) cells; OPPTS 870.5300 [§84-2]

DP BARCODE: D222183 SUBMISSION NO.: S498997

PC CODE: 004006 TOX. CHEM. NO.: MRID NO: 43769703

TEST MATERIAL (PURITY): S-41311 (95.3%)

SYNONYM(S): S-4056F; [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate

CITATION: Hara, M. (1992). In vitro gene mutation test of S-41311 in V79 Chinese hamster cells; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0046; Study Completion Date: August 3, 1992. (Unpublished) MRID NUMBER: 43769703

SPONSOR: Sumitomo Chemical Co., Ltd., Osaka, Japan

EXECUTIVE SUMMARY: In two independently performed mammalian cell gene mutation assays (MRID No. 43769703), Chinese hamster lung fibroblasts V79 cells were exposed to S-41311 (95.3%) over dose ranges of 44.4-150 μg/mL -S9 or 50-200 μg/mL +S9. The S9 homogenate was derived from Kanechlor 400-induced rat livers and the test material was delivered to the test system in dimethyl sulfoxide.

Compound insolubility was noted at ≥175 μg/mL +S9; severe cytotoxicity was seen at ≥125 μg/mL -S9 and 200 μg/mL +S9. The positive controls induced the expected mutagenic responses. There was, however, no evidence that the test material was mutagenic at any dose under any assay condition.

This study is classified as Acceptable and satisfies the guideline requirement for a gene mutation assay (§84-2).

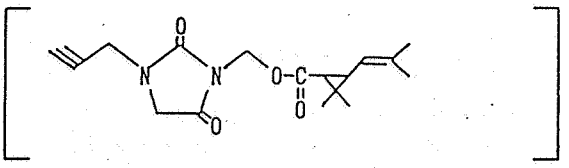
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311

Description: Not provided
Lot/batch number: LO-910802B
Purity: 95.3%
Receipt date: Not reported
Stability: Not listed
CAS number: Not available
Structure:



Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Storage conditions for the test material were not reported. Dosing solutions were prepared immediately prior to use. Analytical determinations were not performed to verify actual concentrations.

2. Control Materials:

Negative: None

Solvent/concentration: DMSO/1%

Positive: Nonactivation (concentrations, solvent): Ethyl methanesulfonate (EMS) was prepared in DMSO to yield a final concentration of 200 µg/mL.

Activation (concentrations, solvent): 9, 10-Dimethyl-1,2-benzanthracene (DMBA) was prepared in DMSO to yield a final concentration of 5 µg/mL.

3. Activation: S9 derived from 6-week old male Sprague-Dawley

____ Aroclor 1254	__x__ induced	__x__ rat	__x__ liver
____ phenobarbital	____ noninduced	____ mouse	____ lung
____ none		____ hamster	____ other
__x__ other (Kanechlor-400)		____ other	

The S9 homogenate was prepared by the performing laboratory and the S9 mix contained the following components:

S9 mix composition:

Component	Concentration
NADPH	4 mM
Glucose 6-phosphate	5 mM
$MgCL_2$	5 mM
KCL	33 mM
HEPES buffer (pH 7.2)	4 mM
S9	30%

Note: One milliliter of the S9 mix was added to 9.0 mL of serum free Eagle's minimum essential medium (EMEM).

4. Test Cells: Mammalian cells in culture

_____ mouse lymphoma L5178Y cells
_____ Chinese hamster ovary (CHO) cells
__x__ V79 cells (Chinese hamster lung fibroblasts)
_____ other (list):

Properly maintained? Yes.
Periodically checked for mycoplasma contamination? Yes.
Periodically checked for karyotype stability? Yes.
Periodically "cleansed" against high spontaneous background? Not reported.

5. Locus Examined:

_____ thymidine kinase (TK)
selection agent: _____ bromodeoxyuridine (BrdU)
(give concentration) _____ fluorodeoxyuridine (FdU)

__x__ hypoxanthine-guanine-phosphoribosyl transferase (HGPRT)
selection agent: _____ 8-azaguanine (8-AG)
(give concentration) 10 µg/mL 6-thioguanine (6-TG)

_____ Na^+/K^+ATPase
selection agent: _____ ouabain
(give concentration)

_____ other (locus and/or selection agent; give details):

6. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Seven concentrations (3.13, 6.25, 12.5, 25, 50, 100 and 200 µg/mL) were evaluated in the absence and presence of S9 activation.

(b) Mutation assay: Two nonactivated and two S9-activated assays were performed; doses were as follows:

(1) Nonactivated conditions:

Trial I: 44.4, 66.7, 100 and 150 μg/mL.

Trial II: 44.4, 66.7, 100 and 125 μg/mL.

(2) S9-activated conditions:

Trial I: 50, 100, 150 and 200 μg/mL.

Trial II: 50, 100, 150 and 175 μg/mL.

B. TEST PERFORMANCE:

1. Cell Treatments:

(a) Cells exposed to test compound or negative and positive controls for:
__5__ hours (nonactivated) __5__ hours (activated)

(b) After washing, cells were cultured for __7__ days (expression period) before cell selection.

(c) After expression, $3x10^5$ cells/dish (10 dishes) were cultured for __7__ days in selection medium to determine numbers of mutants; 100 cells/dish (5 dishes) were cultured for __6__ days in nonselection medium to determine plating efficiency.

2. Statistical Methods: The data were not evaluated for statistical significance.

3. Evaluation Criteria:

Assay validity: For an assay to be considered valid the following criteria must be satisfied: (a) the cloning efficiency (CE) of the solvent controls must be ≥50%; (b) the mutation frequency (MF) for the solvent controls was within ± 3 times the standard deviation (SD) of the historical spontaneous frequency ($0-1.34x10^{-5}$ -S9 or $0-1.35x10^{-5}$ +S9); (c) the positive controls induced a >10-fold increase in the MF compared to the solvent control; (d) the highest test material dose was cytotoxic, the limit of solubility or the recommended high dose for this test system (5000 μg/mL); and (e) the MF for at least three treatment levels could be determined.

Positive response: The test material was considered positive if: (a) the MF of any treatment group was >3-fold higher than the corresponding vehicle control group and greater than the historical background frequency range (i.e., average MF ± 3 x SD), and (2) the response was both dose related and reproducible.

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Test: Concentrations of 3.13-200 μg/mL +/-S9 were initially assessed for cytotoxic effects. Compound precipitation was observed in cultures treated with 200 μg/mL +/-S9. No cells survived exposure to this level in the absence of S9 activation and relative survival (RS) with S9 was 12.3%. For the remaining nonactivated concentrations, RS ranged from 55.3% at 100 μg/mL to ≥95% at ≤50 μg/mL. In the S9-activated phase of the cytotoxicity test, ≥80.1% of the cells survived treatment with levels ≤100 μg/mL. Based on these results, the dose range selected for the initial mutation assay was 44.4-150 μg/mL -S9 and 50-200 μg/mL +S9.

2. Mutation Assays:

(a) Nonactivated conditions: Summarized results from the two independently performed nonactivated mutation assays with S-41311 are presented in Study Report Table 2, p. 20 (see Attachment). As shown, the high dose used in both trials (150 μg/ml--Trial I or 125 μg/mL--Trial II) was severely cytotoxic; the cultures at these levels were not carried further. Results for lower concentrations (≤100 μg/mL) did not suggest a mutagenic effect. Although the MF was elevated at 66.7 μg/mL (Trial I), the increase was not dose related or reproducible and the value fell within the historical control range (0-1.34x10^{-5} mutants/colony forming units) of the reporting laboratory. Similarly, the MF at this dose (10.3x10^{-6} mutants/colony forming units) approximated the expected spontaneous frequency for CHO V79 cells (≤1x10^{-5} mutants/colony forming units)[1].

(b) S9-activated conditions: Summarized findings from the S9-activated phase of the mutation study are presented in Study Report Table 3 (see Attachment), p. 21. In agreement with the preliminary findings, 200 μg/mL +S9 (Trial I) was insoluble and excessively cytotoxic. Insolubility and moderate cytotoxicity (44.9% RS) was also observed at 175 μg/mL (Trial II). There was, however, no indication of a mutagenic response over the concentration ranges selected for the S9-activated trials.

By contrast to the negative results with the test substance, the nonactivated (200 μg/mL EMS) and S9-activated (5 μg/mL DMBA) positive controls induced powerful mutagenic responses in both trials.

Based on the overall findings, the study author concluded that "S-41311 is not mutagenic under the conditions tested."

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[1]Bradley, M.O., Bhuyan, B., Francis, M.C., Langenbach, R., Peterson, A., Huberman, E. (1981). Mutagenesis by chemical agents in V79 Chinese hamster cells: A review and analysis of the literature. Mutat. Res. 87:81-142.

D. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS: We assess that the study author's interpretation of the data was correct. In both the presence and absence of S9 activation, S-41311 was assayed to severly cytotoxic doses (≥125 μg/mL -S9; 200 μg/mL +S9) and/or insoluble levels (≥175 μg/mL +S9) but failed to induce a mutagenic response in two independently performed studies. In addition, the sensitivity of the assay to detect mutagenesis was clearly demonstrated by the results obtained with the positive controls (200 μg/mL EMS -S9 and 5 μg/mL DMBA +S9) in both trials. We conclude, therefore, that S-41311 was adequately tested and found to be nonmutagenic in this well-conducted in vitro mammalian cell gene mutation assay.

D. STUDY DEFICIENCIES: NONE. A typographical error was, however, noted on Study Report, Table 3, p. 21 The concentration of the positive control (DMBA) listed for Trial I (200 μg/mL) is incorrect; the correct concentration should be 5 μg/mL.

Incomplete Application Received

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012119

S-41311 **Repeat Dose Dermal Toxicity (82-2a)**

EPA Reviewer: Sanjivani B. Diwan ,Ph.D. Sanjivani Diwan , Date 10/1/96
Review Section I, Toxicology Branch II (7509C)
EPA Secondary Reviewer: Jess Rowland, M.Sc. J M Rowland, Date 10/1/96
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Repeat Dose Dermal Toxicity - 21 Day [Rat]; OPPTS 870.3200 (rodent) [§82-2a]

DP BARCODE: D222183
P.C. CODE: 004006
MRID NO.: 43750740

SUBMISSION CODE: S498997
TOX. CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): S-41311 (92.9%)

SYNONYMS: Imiprothrin

CITATION: Moore, C.L. (1995). 21-Day Dermal Toxicity Study in Rats with S-41311. Corning Hazleton Inc., Vienna, VA. Study No. SGT-51-0072, May 25, 1995. MRID 43750740. Unpublished.

SPONSOR: Sumitomo Chemical Company, Osaka, Japan

EXECUTIVE SUMMARY: In this 21-day dermal toxicity study, 5 Sprague-Dawley rats/sex/group received topical application with dosages of either 100, 300 or 1,000 mg/kg of S-41311 (2 ml/kg/day) to approx. 5 x 5 cm shaved area, 6 hours per day for 21 consecutive days. Treatment-related signs of dermal toxicity were noted in both sexes at 1,000 mg/kg/day and consisted of increased incidence and/or severity of acanthosis and hyperkeratosis at the site of application. A decrease in body weight gain was observed in males (74% of control) and in females (82% of control) at 1,000 mg/kg/day.

The systemic toxicity LOEL is 1000 mg/kg for males and females based on decrease in body weight gain; the systemic toxicity NOEL is 300 mg/kg.

The dermal toxicity LOEL is 1,000 mg/kg for males and females based on acanthosis and hyperkeratosis of the skin; the dermal toxicity NOEL is 300 mg/kg for males and females.

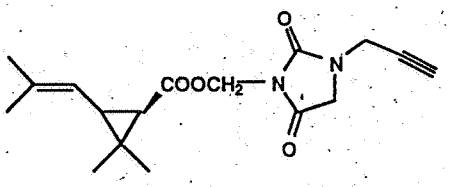
This 21-day dermal toxicity study is classified acceptable, and does satisfy the guideline requirement for a repeated dose dermal toxicity study (82-2a) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. Flagging statement was not required.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311
   Chemical Name: [2,5-dioxo-3-(2-propenyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate,
   Synonym: Imiprothrin
   Description: Light-yellow, thick, viscous liquid
   Lot #: Y-011001
   Purity: 92.9%
   Stability of compound: Test material stable when stored refrigerated in dark
   Structure:



2. Vehicle: Duke's® Pure Corn Oil; Lot No. 4D06

3. Test animals: Rat
   Strain: Sprague-Dawley (Crl: CD®BR)
   Age and weight at study initiation: Approx. 29-day-old;
   Males - 297 to 338 g; Females -166 to 208 g
   Source: Charles River Laboratories, Raleigh, NC
   Housing: Individually in stainless steel cages
   Diet: PMI® Certified Rodent Diet® #5002 ad libitum
   Water: Tap water ad libitum
   Environmental conditions: Temperature: 22±4°C
   Relative Humidity: 55±15%
   Air changes: 10/hour
   Photoperiod: 12 hours light/dark
   Acclimation period: Approx. 14 days

B. STUDY DESIGN:

1. In life dates - start: March 2, 1995
   end: March 24, 1995

2. Animal assignment

   Animals were assigned on a weight basis, using computer generated randomization procedure, to the test groups as shown in table 1.

TABLE 1: STUDY DESIGN

Concentration (mg/kg/day)[b]	Male	Female
Control (0)	5	5
100	5	5
300	5	5
1,000	5	5

3. Dosage Selection

The dosage levels were selected based on the results of an earlier 7-day study conducted to evaluate the potential dermal and systemic toxicity of S-41311 when applied daily for 6 hours to the dorsal skin of Sprague-Dawley rats. In this study, the test material in corn oil was applied to three rats/sex at dose levels of 100, 300, and 1,000 mg/kg/day. No evidence of dermal and systemic toxicity was observed; the NOEL was 1,000 mg/kg/day (limit dose). Based on these results, the same dose levels were selected for the 21-day dermal study to further evaluate the potential dermal and systemic toxicity of S-41311 in rats.

Preparation of Dosing Solution and Analysis

The dosing solutions were prepared daily by heating the test material and vehicle in a water bath at approx. 40°C. The weighed amount of the test chemical was mixed with the vehicle (corn oil) in a precalibrated flask. The contents of the flask were mixed on a magnetic stirrer in a water bath at 70°C until homogeneity was achieved. The dosing solution was covered with aluminum foil and stored in an insulated cooler. The dosing volume for each rat was calculated based on the most recent body weight and a dose factor of 2 ml/kg/day.

Homogeneity and stability analyses were conducted at room temperature on 5 and 500 mg/ml formulations prior to initiation of an earlier 7-day dose range-finding study. For each formulation, the top, middle and bottom portions of the duplicate samples were analyzed for homogeneity. The concentration analyses were performed on a sample from each formulations from the

first mix for all dose levels on Days 1, 8, and 15.

Results - Homogeneity Analysis: 93.0-99.5%
Stability Analysis: 89.5-98.6
Concentration Analysis: 102-106%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable (within 6% of target concentrations).

Preparation of Animal Skin/Compound Administration

The fur on the entire trunk area of each rat (approx. 10 x 6 cm) was shaved 1 week prior to the initiation of dosing. One day prior to the first application, the procedure was repeated. The animals were fitted with a plastic collar at least 5 days prior to initiation of dosing to prevent ingestion of the test substance following treatment. During application of the test material, the test and control dosing solutions were kept on a hot plate (at 40°C). On the day of treatment, both the control and test solutions were applied to an area (approx. 5 x 5 cm) in the dorsothoracic lumbar region with a syringe and spread evenly with a glass rod. The test area was covered with a gauze and sterile surgical tape wrapped around the shaved truck. After six hours, the bandages were removed and the treated areas were washed with distilled water and dried with kleenex. The animals were observed for signs of dermal irritation or systemic toxicity. Dermal irritation was scored using the Draize scale. Control animals were handled similarly except for the substitution of corn oil for the test chemical. The treatments were repeated daily for 21 days.

C. Statistical Analyses

A description of the statistical analyses from the study report is attached to the DER.

D. Experimental Design

The study protocol required the following observations and examinations at the indicated times or frequencies.

mortality and moribundity- twice daily
clinical signs of toxicity and dermal irritation - once daily
body weights - prior to initiation of treatment,

weekly, and at termination
food consumption - weekly intervals during the treatment period
hematology and clinical chemistry - at termination
gross necropsy - all animals
organ weights - designated organs from all animals
histopathology - designated organs and tissues from all animals

D. Urinalysis

Urine analysis was not performed.

E. Sacrifice and Pathology

Animals were fasted overnight prior to clinical sampling. For hematology and clinical chemistry evaluations, blood was drawn from the orbital plexus. The CHECKED (X) hematology parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Erythroblast count	x	Reticulocyte count
X	Platelet count*	x	Absolute reticulocyte count

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical Chemistry

The CHECKED (X) clinical chemistry evaluations were done.

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Albumin/globulin ratio
	Magnesium	X	Blood creatinine*
X	Phosphorus*	X	Blood urea nitrogen*
X	Potassium*	X	Cholesterol
X	Sodium*	X	Globulins
		X	Glucose*
	ENZYMES	X	Total bilirubin
	Alkaline phosphatase (ALK)	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (also SGPT)*		
X	Serum aspartate amino-transferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

Approximately 24 hours after the last treatment, the animals were sacrificed by intraperitoneal injection of sodium pentobarbital and exsanguination. The following CHECKED (X) tissues were preserved. The (XX) organ(s) in addition were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta*	X	Brain*
XX	Salivary glands*	X	Heart*	X	Periph. nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)^{T}
X	Stomach*	X	Lymph nodes*		
X	Duodenum*	XX	Spleen*	X	Pituitary*
X	Jejunum*	X	Thymus*	X	Eyes (optic n.)^{T}
X	Ileum*				
X	Cecum*		UROGENITAL		GLANDULAR
X	Colon*	XX	Kidneys*+		Adrenal gland*
X	Rectum*	X	Urinary bladder*	X	Harderian gland^{T}
XX	Liver*+	XX	Testes*+	X	Mammary gland^{T}
x	Gall bladder*	XX	Epididymides	X	Parathyroids*++
X	Pancreas*	X	Prostate	X	Thyroids*++
		X	Seminal vesicle		
	RESPIRATORY	X	Ovaries		OTHER
X	Trachea*	X	Uterus*	X	Sternum
X	Lung*	X	Vagina	X	Skeletal muscle
	Nose			X	Skin
X	Pharynx			X	All gross lesions and masses*
X	Larynx				

* Required for subchronic studies based on Subdivision F Guidelines
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.
T = required only when toxicity or target organ

Histological examinations were done on the liver, kidneys, spleen, salivary glands, and gross lesions from all animals from the control and high dosage groups. Treated and untreated skin from all animals were processed for microscopic examination.

II. RESULTS

A. Observations :

1. Toxicity - No treatment-related clinical signs of toxicity were observed.

2. Mortality - No mortalities were noted.

B. Body weight and weight gain:

Table 2 summarizes the body weights and body weight changes for the selected time intervals during the study. The body weight gain was lower compared to controls in males (74% of control) and in females (82% of control) at 1,000 mg/kg/day.

Table 2
Body Weights and Body Weight Changes in Rats Treated with S-41311 for 21 Days[a]

Parameter	Dosage Levels (mg/kg/day)							
	Males				Females			
Body weight (g):	0	100	300	1,000	0	100	300	1,000
Week 1	318	316	316	312	191	187	192	188
Week 3	364	364	365	347	225	227	222	216
Body Weight Change (g): Week 1-3	47	48	49	35	34	40	30	28
% of control value	-	102	104	74	-	118	88	82

a Extracted from Tables 3A and 3B (pages 45 and 47) of the study no. 510072.

C. Food consumption :

1. Food consumption - Throughout the treatment period, no compound-related effect on food consumption were noted.

D. Clinical Pathology:

No treatment-related effects on hematological and clinical chemistry parameters were noted.

1. Hematology - A significant increase in the mean absolute reticulocyte count (0.26 millions (MI)/μL versus 0.11 MI/μL in control) was observed among females at 300 mg/kg/day (Table 5; p.53). However, this increase was considered incidental because of lack of dose-response and changes in other hematological parameters measured.

2. Clinical Chemistry - One female from 300 mg/kg/day group had increased alanine aminotransferase activity (119 Units (U)/l versus 37-61 U/l in controls); this finding was not accompanied by changes in other liver analytes and was considered incidental.

E. Sacrifice and Pathology:

1. Organ weight - The mean and absolute organ weight data were comparable among control and treated animals.

2. Gross pathology - Upon gross microscopic examination, incidental findings noted consisted of dark area in the glandular portion of the stomach in the control (2/5 females), 100 (2/5 females), 300 (1/5 male and 1/5 female) and 1,000 (3/5 females) mg/kg/day dose groups. Skin sores were noted in the shaved skin area in the control (1/5 female), 100 (1/5 male and 2/5 females), 300 (2/5 females), and 1,000 (1/5 male and 3/5 females) mg/kg/day dose groups. These sores were caused by the repeated application of the surgical tape.

3. Microscopic pathology - Compound-related microscopic changes in the skin were observed at the site of application in all treated groups. These consisted of acanthosis and hyperkeratosis with occasional necrosis of the epidermal surface. However, the incidence and/or severity of these findings were increased in both sexes only at 1,000 mg/kg/day when compared with controls. These are presented in Table 3. No remarkable findings were seen during histopathological evaluation of the liver, spleen, kidney and

findings were seen during histopathological evaluation of the liver, spleen, kidney and salivary glands in both sexes.

Table 3
Incidence of Histomorphological Findings in Treated Skin from Rats Treated with S-41311 for Twenty-one Days[a]

	Dosage Levels (mg/kg/day)							
Sex	Males				Females			
Group	0	100	300	1,000	0	100	300	1,000
Number Examined	5	5	5	5	5	5	5	5
Acanthosis:								
Minimum	3	4	5	0	5	5	4	2
Slight	0	0	0	5	0	0	0	3
Severity Grade	0.6	0.8	1.0	2.0	1.0	1.0	0.8	1.6
Hyperkeratosis:								
Minimum	4	1	3	3	4	1	0	4
Slight	0	0	0	2	0	0	0	1
Severity Grade	0.8	0.2	0.6	1.4	0.8	0.2	0.0	1.2

a Extracted from Page 36 of study no.510072

IV. DISCUSSION

Dermal application of S-41311 to male and female Sprague-Dawley rats at dosage levels of 0, 100, 300, or 1,000 mg/kg/day for 21 consecutive days produced histomorphological changes in the skin as evidenced by acanthosis and hyperkeratosis accompanied by necrosis at the site of application. The incidence and severity of these changes increased in both sexes at 1,000 mg/kg/day. Treatment-related systemic toxicity was limited to decrease in body weight gain in males (26%) at 1,000 mg/kg/day and in females (≥18%) at ≥300 mg/kg/day.

The systemic toxicity LOEL is 1000 mg/kg for males and females based on decrease in body weight gain; the systemic toxicity NOEL is 300 mg/kg.

The LOEL for dermal toxicity is 1,000 mg/kg/day, based on acanthosis and hyperkeratosis of the skin; the NOEL was 300 mg/kg/day.

Inadvertently Omitted

Page 88 is not included in this copy.

Pages _____ through _____ are not included in this copy.

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012119

S-41311 Subchronic Inhalation Study (82-4)

EPA Reviewer: Sanjivani B. Diwan ,Ph.D. Sanjivani Diwan Date 7/30/96
Review Section I, Toxicology Branch II (7509C)
EPA Secondary Reviewer: Timothy F. McMahon, Ph.D. T.F. McMahon, Date 7/30/96
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Inhalation Toxicity - Rat; OPPTS 870.3465 [§82-4]

DP BARCODE: D222183
P.C. CODE: 004006
MRID NO.: 43750730

SUBMISSION CODE: S498997
TOX. CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): S-41311 (92.9%)

SYNONYMS: Imiprothrin

CITATION: Kawaguchi, S. (1992). A 4-Week Inhalation Toxicity Study of S-41311 in Rats. Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. SGT-20-0056; December 18, 1992. (Unpublished) MRID NUMBER: 43750730.

SPONSOR: Sumitomo Chemical Company, Osaka, Japan

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRID 43750730), Sprague-Dawley rats (10/sex/dose) were exposed by whole body exposure to S-41311 (92.5%) mist aerosol at analytical concentrations of 0, 2.4, 22.0, and 186 mg/m^3 (0, 0.0024, 0.022, and 0.186 mg/l, respectively) for 4 hours/day, 5 days/week for a total of 28 days for males and 29 days for females. The two control groups were exposed to vehicle or air. The median aerodynamic diameter of mist aerosol ranged between 0.80 and 0.86 μm.

Compound-related increase in the incidence of clinical signs including irregular respiration, reduced spontaneous activity, red material around nose, salivation, tip toe gait, nasal discharge and urinary incontinence (in both sexes), jumping, hyperactivity and tremor (in females), increase in reticulocyte count and decreases in hemoglobin, and hematocrit (both sexes), lower MCV and MCHV (in males), and decrease in erythrocyte count (in females), decrease in body weight gain in males (73% of control) and in females (80% of control), dark liver, increased relative liver weights, increased absolute and relative salivary glands weights and hyperplasia of acinous cells of salivary gland in both sexes were observed at 186 mg/m^3. No effects were noted at concentrations of ≤22 mg/m^3. **The LOEL is 186 mg/m^3, based on increased incidence of clinical signs indicating effects on the nervous system, decreases in body weight gain, hemolytic anemia, increase in relative liver weights, dark liver, increase in absolute and relative salivary gland weights and hyperplasia of acinous cells. The NOEL is 22 mg/m^3.**

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This study is acceptable and satisfies the guideline requirement for a subchronic inhalation study (82-4) in the rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No flagging statement was submitted.

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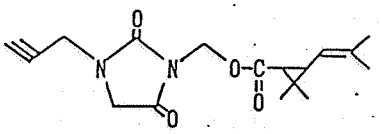
I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311
   Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate,
   Synonym: Imiprothrin
   Description: Clear, yellow-orange oily liquid
   Lot #: Y-011001
   Purity: 92.9%
   Stability of compound: Test material was stable when stored refrigerated in the dark
   CAS NO.: Not available
   Structure:



2. Vehicle: Pure Corn Oil (Nacalai Tesque Inc. Kyoto, Japan)

3. Test animals: Species: Rat
   Strain: Sprague-Dawley (Crj: CD®SD) (SPF)
   Age and weight at study initiation: 6 weeks, Males - 177 to 208 g; Females - 132 to 173 g
   Source: Charles River Japan, Inc., Hino Breeding Center, Shiga, Japan.
   Housing: In aluminum cages; 3 per cage during quarantine; 2 rats of the same sex/cage during the study period
   Diet: Pellet Diet (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) ad libitum except during exposure
   Water: Filtered tap water ad libitum except during exposure
   Environmental conditions: Temperature: 24±2°C
   Relative Humidity: 55±10%
   Air changes: 10/hour
   Photoperiod: 12 hours light/dark
   Acclimation period: 8 days (quarantine for 7 days + acclimation for 1 day). During this period, body weight gain was determined; clinical observations and ophthalmological examinations were performed on all animals.

B. STUDY DESIGN:

1. In life dates - start: October 22, 1991
   end: November 18, 1991

2. Animal assignment

Animals were assigned on a weight basis, using a computer generated randomization procedure, to the test groups as shown in table 1.

TABLE 1: STUDY DESIGN[a]

Test group	Nominal Test Conc. mg/m^3 (mg/L)	Analytical Test Conc. mg/m^3 (mg/L)	MMAD μm	GSA	Rats/sex
Control-1 (Vehicle)	0.0	0.0	0.83	1.75	10
Control-2 (Air)	0.0	0.0	- -	- -	10
Low (LCT)	0.013 (0.000013)	2.4 (0.0024)	0.86	1.67	10
Mid (MCT)	0.133 (0.000133)	22.0 (0.022)	0.80	1.60	10
High (HCT)	1.32 (0.00132)	186 (0.186)	0.82	1.67	10

a Data extracted from study number 20056 and tables 3, 4, and 5 (pages 25-33); and appendices A and B (pages 87-129).

3. Dose Selection

In a preliminary study, male and female rats were exposed to analytical concentrations of 2.7, 34 or 290 mg/m^3 at a rate of about 2 ml/min for 4 hours/day for 5 consecutive days. Compound-related signs of toxicity were noted in both sexes at 290 mg/m^3 and consisted of irregular respiration, reduced spontaneous activity, nasal discharge, red material around nose, salivation, urinary incontinence and tip toe gait; there was slight decrease in body weight gain among females. Males and females at 34 mg/m^3, exhibited irregular respiration and decreased spontaneous activity. No effects were noted at 2.7 mg/m^3. Based on the above findings, the concentrations of 2, 20 and 200 mg/m^3 were selected for the main study.

4. Generation of the test atmosphere and description of the chamber:

During exposure to mist aerosol, five rats were housed individually in each section of an exposure cage (215 cm^2 floor size x 14 cm height) which was installed within a chamber for whole body exposure with a volume of 0.56 m^3.

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The test material was diluted with corn oil and was introduced into the atomizer (AKI Jet 04) by a tube pump (MasterFlex PA-26A) and sprayed under compressed air at 2.0 kg/cm^2. The mist aerosol was introduced into the exposure chamber supplied with an air flow of 0.12 m^3/min using a blower pump and a continuous pressure of -7 mmH_2O. During the four-hour exposure period, the temperature, relative humidity, air flow rate and pressure in the chamber were monitored prior to beginning of exposure, and at 2 and 4 hours after the initiation of exposure. Rats were exposed for 4 hours/day continuously over a period of 28 days for males and 29 days for females. Food and water were withheld from the animals during exposure.

Time to equilibrium was 4 minutes.

Analytical Chemistry

Test atmosphere concentrations were measured twice during each daily exposure. A total amount of 100 L aerosol in the chamber was collected at a rate of 20 L/min using an air sampler connected to a flow meter (Model D-80RG). The aerosol was trapped on silica gel and extracted with acetone and quantified for S-41311 by gas chromatography (Model GC-15A equipped with FID detector; refer to Figure 1 in the attachment). The actual test concentration in the chamber was calculated from the value obtained from the analysis and the amount of air collected. The nominal test concentrations were obtained by dividing the total volume of the test aerosol consumed during exposure with the total amount of air flow into the chamber (0.12 m^3/min x 240 min = 28.8 m^3). Results are reported in table 1 above.

Particle size determination The aerosol was collected through the sampling line and the distribution of particle size was determined twice a week and three times during each exposure using microscopic sedimentation analyzer (Model SA-MID). Approximately 81 to 90% of the particles were found to range in size from 0.986 to 2.090 μm (Appendix B; pages 94-129) and therefore, were within the accepted limit of 1-3μm. The median aerodynamic diameter and log-standard geometric deviation were calculated using computerized Probit analysis. Results are in table 1 above.

5. Statistics

- Body weight, food consumption, water consumption,

hematology and clinical chemistry and organ weight data - One-way Analysis of Variance (ANOVA); the intergroup differences were analyzed by Least Significant Difference Method

- Urinalysis - Kruskal-Wallis test followed by Scheffe's rank sum test
- The incidence of histopathological findings -Fisher's exact probability test; Severity of lesions was analyzed by Mann-Whitney's test.

The Reviewers have no objections to the analyses used.

C. METHODS:

1. Observations:

Animals were observed for clinical signs of toxicity prior to beginning of exposure, then at 2 and 4 hours during exposure, and at one hour following exposure.

2. Body weight

Animals were weighed prior to beginning of exposure and twice weekly thereafter, and on the day of sacrifice.

3. Food and Water Consumption

Food and water consumption were determined once/week/cage (2 rats of the same sex/cage) on these days when the body weights were measured.

4. Ophthalmoscopic examination

Ophthalmoscopic examination of all animals was conducted prior to beginning of the study. In addition, eyes of animals from the vehicle control, air control and 186 mg/m^3 dose groups were examined prior to beginning of 24th exposure.

5. Blood Work:

Blood was collected from the abdominal aorta of fasted animals for hematology and clinical analysis from all animals after about 19 hr, following the final exposure. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Neutrophils (Neut)
X	Hemoglobin (HGB)*	X	Monocytes (Mono)
X	Leukocyte count (WBC)*	X	Eosinophils (Eos)
X	Erythrocyte count (RBC)*	X	Basophils (Baso)
x	Platelet count* (PLT	X	Fibrinogen (Fib)
	Blood clotting measurements*		Leukocyte differential count*
x	(Activated partial thromboplastin time) (APPT)	X	Mean corpuscular HGB (MCH)
	(Thromboplastin time)	X	Mean corpusc. HGB conc.(MCHC)
	(Clotting time and potential)	X	Mean corpusc. volume (MCV)
		X	Reticulocyte count (RET)
X	(Prothrombin time) (PT)	X	Lymphocytes (Lympho)

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium* (Ca)	X	Albumin*
X	Chloride* (Cl)	X	Albumin-globulin ratio (A/G)
	Magnesium	X	Phospholipids (PL)
X	Inorganic Phosphorus* IP)	X	Blood urea nitrogen* (BUN)
X	Potassium* (K)	X	Total Cholesterol (T.Cho)
X	Sodium* (Na)	X	Globulins (α1, α2, β and fractions)
	ENZYMES	X	Glucose* (GLU)
X	Alkaline phosphatase (ALP)	X	Total bilirubin (T. Bil)
X	Alanine amino-transferase (ALT)*	X	Direct bilirubin (D. Bil)
X	Aspartate amino-transferase (AST))*	X	Creatinine* (Cre)
X	Cholinesterase (ChE)	X	Total protein (TP)*
X	Creatine phosphokinase (CPK)	X	Triglycerides (TG)
X	Lactate dehydrogenase (LDH)		
X	Lucine aminopeptidase		
	Gamma glutamyl transferase (GGT)		
X	Gamma glutamyl transpeptidase (GTP)		

* Required for subchronic studies based on Subdivision F Guidelines

6. Urinalysis*

Urine was collected from all males and females from the vehicle control, air control and 186 mg/m^3 dose groups before beginning of the 22nd exposure. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
	Volume	X	Ketones
	Specific gravity	X	Bilirubin
X	pH	X	Blood
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen
	Sodium		
	Potassium		
	Na/K ratio		
	Osmolarity		

* Not required for subchronic studies

7. Sacrifice and Pathology

All animals that were sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. At terminal sacrifice, liver, kidneys, spleen, heart, lungs, brain, thymus, salivary glands, testes, prostate, ovaries, adrenals, pituitary and thyroid were weighed. The (XX) organs, in addition, were processed for histopathology. Periodic Acid-Schiff (PAS) staining was performed on the salivary glands from 2 females from the vehicle control group and 3 females from the 186 mg/m^3 group to assess qualitatively their functional activity.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*
XX	Salivary glands*	XX	Heart*	X	Sciatic nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)[T]
X	Stomach*	X	Lymph nodes*	X	
X	Duodenum*	XX	Spleen*	XX	Pituitary*
X	Jejunum*			X	Eyes (optic n.)[T]
X	Ileum*		UROGENITAL		GLANDULAR
X	Cecum*	XX	Kidneys*+	XX	Adrenal gland*
X	Colon*	X	Urinary bladder*	X	Harderian gland[T]
X	Rectum*	XX	Testes*+	X	Mammary gland[T]
XX	Liver*+	X	Epididymides	X	Parathyroids*
	Gall bladder*	XX	Prostate*	XX	Thyroids*
X	Pancreas*	X	Seminal vesicle	XX	Thymus*
	RESPIRATORY	XX	Ovaries*		OTHER
X	Trachea*	X	Uterus*	X	Femur
XX	Lung*	X	Vagina	X	Sternum
X	Nasal cavity			X	Skeletal muscle
	Pharynx			X	Skin
X	Larynx			X	All abnormal tissue*

* Required for subchronic studies based on Subdivision F Guidelines

+ Organ weight required in subchronic and chronic studies.

T = required only when toxicity or target organ

II. RESULTS

A. Observations : Compound-related increase in clinical signs of toxicity was observed in both sexes at 186 mg/m^3. The majority of the clinical signs seen in both sexes were observed beginning on Day 1 during 4-hour exposure. These consisted of irregular respiration, decrease in spontaneous activity, nasal discharge, salivation, and adhesion of dark red material around the nose. Additional signs were noted from Day 2 to 26. These included tip toe gait (both sexes), jumping, hypersensitivity and tremors (females) and were seen one-hour following exposure. At 22 mg/m^3, irregular respiration and decrease in spontaneous activity were noted on Day 6 only in males (4/10 males) during 4-hour exposure and at 1 hour (1/10 males) following exposure. These findings were not seen during the remaining exposure duration. Because of lack of adverse effect on other parameters they were considered to be incidental.

None of the above clinical signs were seen in 2.4 mg/m^3 and control groups. Clinical signs common to all exposure

groups included wet fur, rough coat, localized scab and localized loss of hair. Localized loss of hair was more frequently seen in females (4/10) at 186 mg/m^3. Histopathology revealed atrophy of hair follicles which was not considered to be biologically significant.

No mortalities were noted during the study period.

B. Body weight and weight gain:

Treatment-related decreases in body weight gain were noted in males at 186 mg/m^3 beginning on Day 8 of exposure; in females the body weight gain was lower throughout the exposure period. For the entire treatment period, the body weight gain was lower in males (73% of control) and in females (80% of control) at 186 mg/m^3. At 2.4 mg/m^3, although the total body weight gain over the entire exposure period was lower in males (90% of controls) compared to that of controls, this findings was not biologically significant due to lack of effect at 22 mg/m^3. Table 3 summarizes the body weights and body weight changes for the selected time intervals during the study. The terminal body weights were lower compared to controls in males (86% of control) and in females (90% of control) at 186 mg/m^3 (refer to Table 6).

C. Food consumption and Water Consumption :

1. Food consumption - No compound-related effect on food consumption was observed. The transient reduction in food consumption observed in males at 186 mg/m^3 on Day 11 (Table 10, pages 46 and 47 of the report) of exposure was considered to be incidental.

2. Water Consumption - No compound-related effect on water consumption was noted (Table 11, pages 48-49 of the report).

D. Urinalysis: No compound-related effects were noted (Tables 12 and 13, pages 50-56).

E. Ophthalmology: No treatment-related changes were observed (Table 14, page 57 of the report).

Table 2
Clinical Signs in Rats
Treated with 186 mg/m3 S-41311 for Four Weeks[a]

Sex (No.of Rats)	Males (10)					Females (10)				
Exposure period (Day 1-28/29)	Day of onset	No. of rats exhibiting signs/time of onset	Last Day with signs observed	No. of rats exhibiting signs/time of onset	Total no. of males exhibiting signs	Day of onset	No. of rats exhibiting signs/time of onset	Last day with signs observed	No. of rats exhibiting signs/time of onset	Total no. of rats exhibiting signs
Irregular respiration[b]	1	10/B	28	8/B	10/10	1	10/B	29	9/B	10/10
Decrease in spontaneous activity[b]	1	7/B	16	1/B	9/10	1	4/B	18	2/B	6/10
Jumping[c]	-	-/-	-	-	-	16	1/C	-	-	1/10
Hypersensitivity[c]	-	-/-	-	-	-	26	1/C	-	-	1/10
Tremor[c,d]	-	-/-	27	1/C	3/10	15	1/C	26	1/C	1/10
Tip toe gait	20	2/C	27	1/B	3/10	2	2/C	29	2/C	6/10
Nasal discharge	1	1/B	2	2/B	2/10	1	4/B	3	2/B	4/10
Bleeding	1	1/C	28	1/C	1/10	-	-	-	-	-
Red material around snout	1	2/C	26	1/C	4/10	1	5/C	26	1/C	8/10
Salivation	1	2/B	20	2/C	2/10	1	2/B	-	-	3/10
Urinary Incontinence	20	1/C	23	1/C	1/10	2	1/C	23	1/C	3/10

a Extracted from Table 8 (pages 36 and 43) of study no. 200056; the animals were observed for clinical signs prior to exposure, at 2 and 4 hour during exposure and at 1 hour following exposure.
b Observed with greater frequency and longer duration
c observed sporadically
d observed only on one day
B = During 4-hour exposure;C =One-hour following exposure

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Table 3
Body Weights and Body Weight Changes in Rats
Treated with S-41311 for Four Weeks[a]

Parameter	Dosage Levels (mg/m3)									
	Males					Females				
Body weight (g):	C-1	C-2	2.4	22	186	C-1	C-2	2.4	22	186
Day 1	194 ±7.4	192 ±9.3	193 ±7.0	194 ±8.2	193 ±7.7	154 ±8.6	153 ±7.2	153 ±7.3	154 ±10.4	155 ±11.2
Day 28	391 ±11.6	395 ±25.8	370 ±23.6	376 ±26.7	338** ±32.5	244 ±24.4	252 ±19.5	241 ±15.7	246 ±19.0	226 ±18.6
Body Weight Change (g): Day 1-28	198 ±9.5	203 ±17.7	178* ±19.3	182 ±22.6	145** ±27.3	90 ±18.3	99 ±15.5	88 ±9.9	93 ±10.8	72** ±11.4
% of control value[b]	-	-	90	92	73	-	-	98	103	80

a Extracted from Table 9 (pages 44 and 45) of study no. 200056; C-1 = Vehicle control, C-2 = Air control.
b Calculated by the reviewer.
* Significantly different from controls, $p<0.05$; $p<0.01$

F. Blood work: Compound-related effects on hematological and clinical chemistry parameters were noted.

1. Hematology - Compound-related changes in several hematological parameters indicative of slight anemia were noted in both sexes at 186 mg/m^3. The key hematology findings are summarized in Table 4.

Among treated males, the following significant changes from the vehicle control were noted: decreases in hemoglobin (5%) and hematocrit values (6%), increase in reticulocyte count (27%), and a lower mean corpuscular volume (5%) and hemoglobin concentration (5%).

Somewhat similar changes were noted in females that included decreases in hemoglobin (9%) and hematocrit values (8%), lower erythrocyte count (7%), increased reticulocyte count (87%) and prolongation of activated partial thromboplastin time at 186 mg/m^3.

Other significant changes noted in both sexes included lower fibrinogen value in males at ≥2.4 mg/m^3. Decreased monocyte count in males and higher platelet count in females were noted at 2.4 mg/m^3. Because of lack of dose-response, these changes were considered to be unrelated to treatment.

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2. Clinical Chemistry - Compound-related changes were noted in several clinical chemistry parameter at 186 mg/m^3 compared to vehicle control group. The key findings are presented in Table 5 and are discussed below.

For males at 186 mg/m^3, there were increases in β-globulin (14%), total cholesterol (22%), and γ-glutamyl transpeptidase activity (1%) and decreases in α1-globulin (18%), glucose (14%) and triglyceride levels (56%).

For females at 186 mg/m^3, there was significant increase in β-globulin (11%) and a decrease in α1-globulin level (11%) and cholinesterase activity (37%).

Table 4
Selected Hematology Parameters in Rats
Treated with S-41311 for Four Weeks[a]

	Dosage Levels (mg/m3)									
	Males					Females				
Parameters	C-1	C-2	2.4	22	186	C-1	C-2	2.4	22	186
RBC (X10^6/μl	7.58	7.51	7.65	7.44	7.52	7.64	7.68	7.83	7.88	7.13** (-7)[b]
ret (x10^4/μL)	21.46	19.99	20.56	19.86	27.20** (+27)	17.71	16.68	20.11	19.88	33.13** (+87)
HGB (g/dl)	14.5	14.6	14.6	14.6	13.8** (-5)	14.7	14.7	14.8	14.0	13.4** (-9)
HCT (%)	40.8	40.5	41.2	40.4	38.5** (-6)	40.6	40.5	41.4	41.3	37.2** (-8)
MCV (fl)	53.8	53.9	53.9	54.3	51.3** (-5)	53.2	52.7	53.0	52.4	52.2
MCH (pg)	19.2	19.5	19.1	19.6	18.3** (-5)	19.2	19.2	19.0	18.0	18.8
APTT (sec)	21.4	22.4	22.8	22.4	23.4	18.8	18.1	18.4	18.4	19.8* (+5)
Fib (mg/dl)	229.6	206.4** (-10)	215.6* (-6)	214.4* (-7)	215.4* (-6)	176.9	184.6	179.8	174.8	176.9

a Extracted from Table 15 (page 58-61) of study no. 200056
b Percent change
C-1 = Vehicle cntrol; C-2 = Air control
Significantly different from controls (C-1 and C-2);*= p<0.05;
**= p<0.01

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Although the triglyceride level was lower in males at 2.4 and 22 mg/m^3, the values were comparable with that of the air control group and were within the normal range. In females, glucose level was higher at 22 mg/m^3 and lower at 186 mg/m^3; because of lack of dose-response, these changes were considered to be incidental. The alkaline phosphatase level was lower in males at 22 mg/m^3 and in both sexes at 186 mg/m^3. However, this enzyme activity was also lower in air control group and therefore, these changes were not biologically significant. The findings of decreased phospholipid and aspartate aminotransferase levels in males at 22 mg/m^3 were considered to be incidental.

Table 5
Selected Clinical Chemistry Parameters
in Rats Treated with S-41311 for Four Weeks[a]

	Concentration levels (mg/m3)									
	Males					Females				
Parameters	C-1	C-2	2.4	22	186	C-1	C-2	2.4	22	186
TG (mg/dl)	75	47** (-37)	47** (-37)	57* (-24)	33** (-56)	18	15	17	21	16
PL (mg/dl)	100	83** (-17)	90	87*	111	92	89	89	96	106
T.Cho (mg/dl)	65	55	56	58	79** (+22)	56	56	56	61	67
ALT (U/l)	47	35** (-26)	46	42*	48	36	27** (-25)	40	38	36
AST (U/l)	123	95** (-23)	116	136	116	129	128	130	139	136
ALP (U/l)	256	184** (-28)	245	222* (-13)	205** (-20)	143	105** (-27)	149	129	117** (-18)
ChE (U/l)	702	640	672	721	632	2565	3067	2427	2237	1605* (-37)
Γ-GTP (U/l)	0	0	0	0	1**	2	2	2	2	2
α 1-GLB (%)	19.7	19.7	18.9	18.6	16.1** (-18)	13.9	14.9	14.1	13.6	12.4** (-11)
β-GLB (%)	15.8	15.0	15.9	15.7	18.0** (+14)	14.3	14.9	14.6	14.8	15.9** (+11)
GLU (mg/dl)	130	150** (+15)	127	125	112** (-14)	116	118	122	128** (+10)	108* (-7)

a Extracted from Table 16 (page 62-66) of the study no.200056
b Values in parenthesis represents percent change
C-1 = Vehicle control; C-2 = Air control
* $p<0.05$;** $p<0.01$

G. Sacrifice and Pathology:

1. Organ weight - The organ weight data are summarized in Table 6. The significant increases in absolute and relative organ weights over the control groups were as follows:

When compared with the vehicle control group, there was increase in relative liver and kidney weights and absolute and relative salivary gland weights in both sexes, increase in relative lung and testis weights in males as well as relative ovary weights in females at 186 mg/m^3. In addition, increases were also noted in relative thyroid weight in males at 2.4 mg/m^3 and relative heart and adrenal weights in females at 2.4 and 186 mg/m^3.

At 186 mg/m^3, changes that were considered secondary to the lower body weights included decrease in absolute brain weight (males) and increase in relative brain weight (males and females), decrease in absolute thymus weight (males and females), prostate, adrenal and pituitary weights (males).

Table 6
Absolute and Relative Weights of Selected Organs from Rats Treated with S-41311 for Four Weeks[a]

	Concentration levels (mg/m3)									
	Males					Females				
Organ Wts.	C-1	C-2	2.4	22	186	C-1	C-2	2.4	22	186
Liver										
Abs	11.48	11.09	10.47	10.79	11.25	6.98	6.70	7.03	7.16	7.54
Rel	3.24	3.08*	3.11	3.15	3.69**	3.09	2.94*	3.20	3.20	3.75**
Kidneys										
Abs	2.78	2.88	2.66	2.77	2.68	1.80	1.93	1.85	1.85	1.88
Rel	0.79	0.80	0.79	0.81	0.88**	0.80	0.83	0.84	0.83	0.93**
Heart										
Abs	1.28	1.22	1.25	1.24	1.18	0.86	0.87	0.93	0.89	0.89
Rel	0.36	0.34	0.37	0.37	0.39	0.38	0.38	0.42**	0.40	0.44**

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Table 6 (Continued)

	Concentrations levels (mg/m^3)									
Organ Wts.	Male					Female				
Lungs										
Abs	1.44	1.41	1.35	1.42	1.33	1.15	1.13	1.16	1.15	1.08
Rel	0.40	0.39	0.40	0.41	0.44**	0.52	0.49	0.53	0.52	0.53
Brain										
Abs	2.00	2.03	1.96	2.01	1.91*	1.88	1.88	1.93	1.90	1.87
Rel	0.56	0.56	0.58	0.59	0.63**	0.85	0.82	0.88	0.85	0.93**
Thymus										
Abs	0.54	0.62	0.52	0.57	0.45*	0.57	0.57	0.51	0.50	0.44**
Rel	0.15	0.17	0.15	0.17	0.15	0.26	0.25	0.24	0.22	0.22
Salivary glands										
Abs	0.65	0.71	0.70	0.67	0.90**	0.46	0.45	0.48	0.46	0.65**
Rel	0.19	0.20	0.21	0.20	0.30**	0.21	0.20	0.22	0.21	0.32**
Testes/Ovaries										
Abs	3.03	3.12	3.08	3.08	3.05	97	99	90	89	96
Rel	0.85	0.87	0.92	0.90	1.01**	42.9	42.9	40.9	40.0	47.8*
Adrenals										
Abs	70	65	68	68	61**	69	69	76	74	73
Rel	19.8	18.0	20.2	20.1	20.2	30.7	29.8	34.5*	33.2	36.5**
Thyroids										
Abs	22	25	24	25	25	21	21	21	20	18
Rel	6.1	6.8	7.2*	7.3*	8.0**	9.4	9.0	9.5	8.8	9.1
Terminal Body Weights										
	355	360	337	342	305**	225	231	219	224	202**
% of Control[b]	--	--	95	96	86	--	--	97	99	90

a Extracted from Tables 17 and 18 (pages 70-78) of the study no. 200056
b Calculated by the reviewer
Abs= Absolute organ weight; Rel=Relative organ weight
* $p<0.05$; ** $p<0.01$

2. Gross pathology - Upon gross pathological examination, compound-related changes noted at 186 mg/m^3 consisted of dark liver in 5/10 males and 3/10 females (vs 0/10 in control) and localized hair loss in 4/10 females (vs 0/10 control). The other changes such as reticular pattern, diaphragmatic nodule and gray white spots in the liver, brown and or red spots in the lungs and nodes in spleen occurred in a non-dose related manner and therefore, were not considered to be treatment-related.

3. Microscopic pathology - Compound-related changes in the salivary glands observed in both sexes consisted of slight densely basophilic staining of acinous cells in the submaxillary and sublingual glands in 9/10 males and 10/10 females of the 186 mg/m^3 group (vs 0/10 in control in both sexes) (Table 20; page 81 of the study report). PAS staining failed to reveal any differences from that of vehicle control group suggesting lack of functional differences. Incidental slight changes were observed in various organs including liver, brain, kidney, spleen, thymus, pancreas, urinary bladder, prostate, epididymis, uterus, skin and brain. These changes were not biologically significant. No remarkable changes were noted in other organs examined.

IV. DISCUSSION

A. Inhalation exposure of 10 male and 10 females Sprague-Dawley rats to S-41311 analytical concentrations at 0, 2.4, 22, or 186 mg/m^3 (0, 0.0024, 0.022, or 0.186 mg/l, respectively) for 4 hours/day, 5 days/week for 4 weeks produced adverse effects at 186 mg/m^3. The clinical signs observed included irregular respiration, decreased spontaneous activity, nasal discharge, red material around nose, salivation and tip toe gait in both sexes and tremor, jumping, and hypersensitivity in females at 186 mg/m^3. Although these findings were accompanied by increase in relative brain weights in males and females and were indicative of neurological effects, they were not severe enough to cause histopathological alteration in the nervous system. Moreover, the changes in brain weight were possibly secondary to lower body weight of the animal.

The evaluation of body weight gain data indicated significant decrease in body weight gain at 186 mg/m^3 in males (73 % of control) and in females (80% of control) over the entire study duration.

Compound-related effects of indicative of hemolytic anemia were noted in both sexes at 186 mg/m^3 as evidenced by decrease in hematocrit, hemoglobin and MCV and MCHC (males), decrease in erythrocyte count and prolongation of activated

partial prothrombin time (in females); increase in reticulocyte count was considered to be in response to anemia. Because of lack of deposition of hemosiderin pigment deposition in the liver and spleen and absence of histopathological findings in bone marrow examination, the anemia observed was considered to be less severe. At 186 mg/m^3, interference in protein and lipid metabolism in the liver was indicated by increase in B-globulin, and total cholesterol levels and γ-glutamyl transpeptidase activity as well as decrease in α1-globulin, glucose, and triglyceride levels. These findings along with the presence of dark liver and increase in relative liver weights were possibly associated with adverse effects on the liver. However, these changes were considered to be adaptive in nature as they were not accompanied by severe changes in liver histopathology such as necrosis or hepatocellular degeneration. Increase γ-GTP was not associated with changes in the histopathology of bile duct.

At 186 mg/m^3, the histopathology revealed dense basophilic staining of acinous cells of maxillary and sublingual glands. This observation indicated hyperplasia of acinous cells of the salivary glands which possibly resulted from an increase in the absolute and relative weights of salivary glands. Furthermore, no differential staining was revealed during the PAS test which would have indicated functional differences between the test and vehicle control groups. Thus, the biological significance of this finding can not be determined. Changes in absolute and or relative weight of several organs were noted. But these changes were not accompanied by meaningful histopathological changes and they were considered to be unrelated to compound exposure.

The LOEL in both sexes is considered to be 186 mg/m^3 (0.186 mg/l), based on clinical signs suggestive of effects on the nervous system, decreases in body weight gain, anemia, dark liver, increased relative liver weights, increased absolute and relative salivary gland weights and hyperplasia of acinous cells of salivary glands in both sexes. The NOEL in both sexes is considered to be 22 mg/m^3 (0.022 mg/l).

B. Study Deficiencies: The following deficiencies were noted:

- During the study period two rats were housed in each cage.
- The urinalysis and opthalmoscopic examinations were conducted on Day 22 and 24 of treatment, respectively. No rationale was provided for the selection of the above timings.

However, the above deficiencies did not adversely impact upon the outcome of the study results.

Imidacloprid Review

Page 108 is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

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_____ Information about a pending registration action.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

S-41311 **Subchronic Oral Study (82-1a)**

EPA Reviewer: Sanjivani B. Diwan ,Ph.D. Sanjivani Diwan Date 7/30/96
Review Section I, Toxicology Branch II (7509C)
EPA Secondary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy ,Date 7/30/96
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity [Feeding]-[Rat]; OPPTS 870.3100 (rodent) [§82-1a]

DP BARCODE: D222183
P.C. CODE: 004006
MRID NO.: 43769702

SUBMISSION CODE: S498997
TOX. CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): S-41311 (92.9%)

SYNONYMS: Imiprothrin

CITATION: Adachi H. (1992). Three-month Subacute Toxicity Study of S-41311 by Dietary Administration in Rats. Sumitomo Chemical Company, Ltd., Osaka, Japan; Study No. 2323; Unique Study ID. No. 200040; May 19, 1992. (Unpublished) MRID NUMBER: 43769702.

SPONSOR: Sumitomo Chemical Company, Osaka, Japan

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID# 43769702), S-41311 (92.9% a.i.) was administered in the diet to male and female Charles River Japan Sprague-Dawley rats (12/sex/dose) at dosage levels of 0, 100, 3,000, 6,000, and 10,000 ppm (0, 5.9, 178.6, 350.4 or 611.2 mg/kg/day in males and 6.7, 196.6, 399.0 or 657.0 mg/kg/day in females, respectively) for three months.

Compound related effects included a decrease in body weight gain and food consumption, and hemolytic anemia in males and females at ≥3000 ppm. In addition, liver changes consisting of hepatocellular hypertrophy, and eosinophilic hepatocytes were noted in both sexes at 10,000 ppm. No adverse effects on survival, clinical signs and ophthalmology were noted.

The LOEL is 3,000 ppm (178.6 mg/kg/day in males and 196.6 mg/kg/day in females) based on decreases in body weight gain, food consumption and hemolytic anemia.

The NOEL for both sexes is 100 ppm (5.9 and 6.7 mg/kg/day in males and females, respectively).

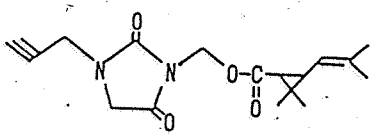
This subchronic toxicity study is classified acceptable, and satisfies the guideline requirement for a subchronic oral study (82-1a) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311
   Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate,
   Synonym: Imiprothrin
   Description: A clear, yellow-orange, oily liquid (MRID # 43750730)
   Lot #: Y-011001
   Purity: 92.9%
   Stability of compound: Neat test material stable at room temperature or at 0-10°C in the dark
   Structure:



2. Vehicle: Basal Diet

3. Test animals: Rat
   Strain: Sprague-Dawley (Crj: CD)
   Age and weight at study initiation: Approx. 5 weeks; Males - 127 to 156 g; Females - 98 to 131 g
   Source: Charles River Japan Inc., Shiga, Japan
   Housing: Two rats of the same sex per cage
   Diet: Commercial Rodent Diet (CRF-1, Oriental Yeast Co., Ltd. Tokyo, Japan) ad libitum
   Water: Tap water ad libitum
   Environmental conditions: Temperature: 24±2°C; Relative Humidity: 55±10%; Air changes: 10/hour; Photoperiod: 12 hours light/dark
   Acclimation period: Approx. 8 days

B. STUDY DESIGN:

1. In life dates - start: April 3, 1991
   end: July 3, 1991

2. Animal assignment

   Animals were assigned to the test groups on a weight basis, using a computer generated randomization procedure (see Table 1).

TABLE 1: STUDY DESIGN

Dietary Concentration (ppm)	Male	Female
Control (0)	12	12
100	12	12
3,000	12	12
6,000	12	12
10,000	12	12

3. Diet preparation and analysis

The diet premix was prepared every four weeks by mixing appropriate amounts of test substance (melted at 60-70°C) with basal diet using a hot mortar. This premix was mixed with the remaining basal diet by automatic mixer, Dalton 250DM-QR, for 15 minutes. All test diet mixtures were stored in polyethylene bags at 0-10°C in the dark until analyzed. At the start of the study, the test compound in the diet samples were analyzed for homogeneity and stability. The top, middle, and bottom portions of the test diet samples at each concentration were analyzed for homogeneity. The concentration analyses were conducted on two occasions (March 26-28 and August 6-7, 1991; Report Appendix 13.1, pages 14-1-33 and 14-1-35).

Results - The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

The stability analyses of the 50 and 10,000 ppm diet samples revealed that the test compound was stable in the diet at least for 6 weeks at 0-5°C (range: 90%-92% and 94%-96%, respectively) and for 2 weeks at room temperature (range: 86%-92% and 93%-95%, respectively; Report Appendix 12, page 14-1-25 to 14-1-27).

Analyses for homogeneity of the 100, 1,000, 3,000, 6,000 and 10,000 ppm diet formulations showed that the mean concentration of S-41311 in the top, middle and bottom portions of the samples was within 7% of the intended concentration (range: 93%-101%, 101%-105%, 100%-103%, 97%-101% and 98%-101%, respectively; Report Appendix 13-1, page 14-1-37).

The concentration analyses of the above diets showed that the percents of the intended S-41311 concentration in each of the above diet formulations were within ±17% (range: 90%-97%, 83%-107%, 93%-105%, 93%-104% and 96%-99% for the 100, 1,000, 3,000, 6,000 and 10,000 ppm groups, respectively; Report Appendix 13-1, page 14-1-38).

The purity of the test compound at study initiation and termination was 92.9% and 93.2%, respectively (Report Appendix 14, page 16-1).

The dose levels selected for this study were based on the results of an earlier one-month dietary rat study in which anemia and hepatic changes, including hepatocellular hypertrophy and eosinophilic hepatocytes were observed at dosages of 1,000, 3,000 and 10,000 ppm; the body weight gain was decreased at 3,000 and 10,000 ppm (Report page 18). Based on these results, the dosages of 3,000, 6,000, and 10,000 (HDT) ppm were selected for this study in anticipation of a dose-response regarding the above findings. The lowest dose of 100 ppm was selected to represent a no-observable-adverse effect level (NOAEL).

4. Statistics - The significance of inter-group differences in body weight, food consumption, hematology, blood chemistry and organ weight data and results of bone marrow examination were assessed by One-Way analysis of variance. Results of urinalysis were assessed by Scheffe's mean rank test followed by Kruskal-Wallis' H-test. The statistical significance of the incidences of clinical signs were analyzed by the Chi-square test (Report page 27).

C. METHODS:

1. Observations:

Animals were observed at least once daily for signs of toxicity, mortality and moribundity.

2. Body weight

Animals were weighed prior to the beginning of treatment, once weekly thereafter and before necropsy.

3. Food consumption and compound intake

Food consumption per cage was determined weekly and is presented as g food/animal/day. Food efficiency

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(relative food consumption in g/kg/day) and compound intake (mg/kg/day) values were calculated from the body weight and food consumption data.

4. Ophthalmoscopic examination

The report stated that ophthalmoscopic examination was conducted on all animals prior to start of the study. Eyes of six animals/sex/group were examined at Week 12 using an ophthalmoscope, an indirect ophthalmoscope and a fundus camera.

5. Blood Work:

Blood was collected under anesthesia from the abdominal aorta of all rats (animals fasted overnight) for hematology and clinical chemistry analysis. The CHECKED (X) parameters were examined. In addition, a femur was removed from 6 animals/sex/group after 13 weeks of treatment; smears of bone marrow were examined microscopically and the myeloid/erythroid ratio was calculated in both sexes of the control and 10,000 ppm groups.

a. Hematology

X	Hematocrit (HCT)*	X	Neutrophils (Neut)
X	Hemoglobin (HGB)*	X	Monocytes (Mono)
X	Leukocyte count (WBC)*	X	Eosinophils (Eos)
X	Erythrocyte count (RBC)*	X	Basophils (Baso)
x	Platelet count* (PLT	X	Fibrinogen (Fib)
	Blood clotting measurements*		Leukocyte differential count*
x	(Activated partial thromboplastin time) (APPT)	X	Mean corpuscular HGB (MCH)
-	(Thromboplastin time)	X	Mean corpusc. HGB conc.(MCHC)
X	(Clotting time and potential)	X	Mean corpusc. volume (MCV)
X	(Prothrombin time) (PT)	X	Reticulocyte count (RET)
		X	Erythroblast count (EBL)
		X	Lymphocytes (Lympho)

* Required for subchronic studies based on Subdivision F Guidelines
"-" = not examined

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b. Clinical Chemistry

	ELECTROLYTES
X	Calcium* (Ca)
X	Chloride* (Cl)
-	Magnesium
X	Inorganic Phosphorus* IP)
X	Potassium* (K)
X	Sodium* (Na)

	ENZYMES
X	Alkaline phosphatase (ALP)
X	Serum alanine amino-transferase (also SGPT or ALT)*
X	Serum aspartate amino-transferase (also SGOT or AST))*
X	Plasma Cholinesterase (ChE)**
-	Creatine phosphokinase (CPK)
X	Lactate dehydrogenase (LDH)
	Gamma glutamyl transferase (GGT)
	Gamma glutamyl transpeptidase (GTP)

	OTHER
X	Albumin*
X	Albumin-globulin ratio (A/G)
X	Phospholipids (PL)
X	Blood urea nitrogen* (BUN)
X	Total Cholesterol (T.Cho)
X	Globulins
X	Glucose* (GLU)
X	Total bilirubin (T. Bil)
X	Direct bilirubin (D. Bil)
X	Creatinine* (Cre)
X	Total protein (TP)*
X	Triglycerides (TG)
X	Serum protein Fractionation

* Required for subchronic studies based on Subdivision F Guidelines
** Refer to memo by Sumitomo dated 9/25/96
"-" = not examined

6. Urinalysis*

Urinalysis was conducted twice during weeks 12 through 13. Fresh urine was collected (metabolism cages in the A.M.) from animals (6/sex/group). Subsequently, urine samples were collected from the same animals after overnight fasting. The CHECKED (X) parameters were examined.

-	Appearance
X	Volume
-	Specific gravity
X	pH
-	Sediment (microscopic)
X	Protein
X	Sodium
X	Potassium
X	Na/K ratio
X	Osmolarity

X	Glucose
X	Ketones
X	Bilirubin
X	Blood
-	Nitrate
X	Urobilinogen

* Not required for subchronic studies
"-" = not examined

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7. Sacrifice and Pathology

All animals that were sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Histopathological examination was conducted on all tissues of both sexes in the 0, and 10,000 ppm groups. In addition, the following were examined in the 100, 3,000, and 6,000 ppm groups: liver, kidneys, lungs, spleen, bone marrow, salivary glands and macroscopically abnormal tissues. At terminal sacrifice, the (XX) selected organs (adrenals, kidneys, liver, spleen, heart, brain, pituitary, thymus, prostate, ovaries, testes, parathyroids/thyroids) were weighed and the weights were expressed as absolute and relative to body weights.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Sciatic nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)[T]
X	Stomach*	X	Lymph nodes*		
X	Duodenum*	XX	Spleen*	XX	Pituitary*
X	Jejunum*	XX	Thymus*		
X	Ileum*				GLANDULAR
X	Cecum*		UROGENITAL	XX	Adrenal gland*
X	Colon*	XX	Kidneys*+	X	Harderian gland[T]
X	Rectum*	X	Urinary bladder*	X	Mammary gland[T]
XX	Liver*+	XX	Testes*+	XX	Parathyroids*
-	Gall bladder*	X	Epididymides	XX	Thyroids*
X	Pancreas*	XX	Prostate*		
	RESPIRATORY	X	Seminal vesicle		OTHER
X	Trachea*	XX	Ovaries*	X	Sternum
X	Lung*	X	Uterus*	X	Femur
-	Nose	X	Vagina	X	Skeletal muscle
-	Pharynx			X	Skin
-	Larynx			X	Eye balls
				X	All abnormal tissue*

* Required for subchronic studies based on Subdivision F Guidelines

+ Organ weight required in subchronic and chronic studies.

T = required only when toxicity or target organ

"-" = not examined

II. RESULTS

A. Observations :

1. Toxicity - No treatment-related clinical signs of toxicity were observed.

2. Mortality - No mortalities were noted.

B. Body weight and weight gain:

At ≥3,000 ppm, treatment-related statistically significant ($p<0.05$ or 0.01) decreases in body weight gain were noted in males and females, over the entire three-month treatment period. Body weights were lower in males at ≥6,000 ppm and in females at ≥3,000 ppm over the same period (see Report Table 2-1, pages 72-77). Table 2 summarizes the body weights and body weight changes for the selected time intervals during the study.
For males and females at ≥3,000 ppm, the body weight gain was lower compared to control (males: 78-91% of control; females: 83-90% of controls) over the entire study period (Day 1-91). The body weight gain in females was also lower (89% of control) at the 100 ppm dosage level. This decrease primarily resulted from significantly lower body weights from days 77-91 (Report page 76) which were accompanied by decreases in food consumption. However, these findings were considered incidental because of a lack of effect in hematology, clinical chemistry, and gross and histopathological examinations.

The study author reevaluated the effect of S-41311 on body weight and body weight gain of rats using data from a six-month study (Report Addendum 2, page 21-1 and 21-2). Contrary to the findings in this three-month study, there were no significant changes in the mean body weights and body weight gains noted in either sex treated with S-41311 for up to six months. However, no details on the study conduct were provided. Therefore, the data from the six-month study could not be used to assess the effect of the test compound on the above stated parameters.

Table 2
Body Weights and Body Weight Changes in Rats
Treated with S-41311 for Thirteen Weeks[a]

Parameter	Dosage Levels (ppm)									
	Males					Females				
Body weight (g):	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
Day 1	143	146	143	143	142	115	117	116	115	115
Day 91	531	516	497	457**	477**	304	286*	286*	271**	271**
Body Weight Change (g): Day 1-91	389	371	354*	314**	305**	189	169*	170*	156**	157**
% of control value[b]	-	95	91	81	78	-	89	90	83	83

a Extracted from Tables 2-1 and 2-2 (pages 72-85) of the study no. 200040.
b Calculated by the reviewers
Significantly different from controls;*= $p<0.05$; **= $p<0.01$

C. Food consumption and compound intake :

1. Food consumption - The food consumption (g/rat/day) and food efficiency (relative food consumption; g/kg/day) data are summarized in Table 3. Compound-related effects on food consumption were noted during the first week of treatment. During this period of treatment, the food consumption was significantly lower compared to controls for males (60-90% of control) and for females (67-87% of control) at ≥3,000 ppm. The relative food consumption was also lower for both sexes at ≥3,000 ppm. Although the food consumption for the subsequent duration remained lower, the relative food consumption was unaffected.

Table 3
Food Consumption (g/rat/day) and Food Efficiency (g/kg/day) in Rats Treated with S-41311 for Thirteen Weeks[a]

	Dosage Levels (ppm)									
	Males					Females				
Parameters	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
Food Consumption (g/rat/day): Day 8	20	20	18*	15**	12**	15	15	13**	11**	10**
% of Controls[b]	--	100	90	75	60	--	100	87	73	67
Day 91	23	22	22	20**	20**	17	15	15	15	15
% of Controls[b]	--	96	96	87	87	--	88	88	88	88
Food Efficiency (g/kg/day): Day 8	98	97	94**	84**	74**	100	98	89**	83**	77**
Day 91	43	43	44	43	46**	54	54	53	54	53

a Extracted from Table 3-1 and 3-2 (pages 86-93) of the study no. 200040
b Calculated by the reviewer
Significantly different from controls; *= $p<0.5$; **= $p<0.01$

2. Compound consumption - The average daily consumption of S-41311 in mg/kg/day, based on the target concentrations, was 5.9, 178.6, 350.4 or 611.2 in males and 6.7, 196.6, 399.0 or 657.0 in females at 100, 3,000, 6,000 and 10,000 ppm, respectively (Report Table 4, pages 97 and 101).

D. Ophthalmology: No treatment-related changes were observed.

E. Blood work: Treatment-related effects on hematological and clinical chemistry parameters were noted.

1. Hematology - Compound-related changes in several hematological parameters indicative of hemolytic anemia were noted in both sexes at ≥3,000 ppm. The selected hematology findings are summarized in Table 4.

Among treated males, significant changes were noted in the following parameters: decreased hemoglobin concentration and hematocrit values at ≥3,000 ppm; decrease in red cell count and increase in reticulocyte count and reticulocyte percentage (number of reticulocytes/total number of blood cells x 100) at 10,000 ppm; increased leucocyte count, lymphocytes and basophils at ≥6,000 ppm; increased neutrophils at 10,000 ppm; and extended prothrombin time as well as activated partial thromboplastin time at ≥6,000 ppm.

Somewhat similar changes were noted in females that included decreased hematocrit values at ≥3,000 ppm; decreased hemoglobin concentration at ≥6,000 ppm; decreased red cell count at 10,000 ppm; increased reticulocyte count at ≥3,000 ppm; increase in percentage of reticulocytes at ≥6,000 ppm; increased MCHC, platelet count and fibrinogen at 10,000 ppm.

Other parameters had significant changes but, because of a lack of a dose-response, were not considered to have been related to test article administration.

Upon examination of bone marrow, no treatment-related differences were noted among control and high-dose animals (M/E ratio: Males: 0.95 versus 1.09 in control; Females: 0.92 versus 0.89 in controls). Therefore, no microscopic examination of bone marrow from other dose group animals was performed.

2. Clinical Chemistry - Compound-related changes were noted in several clinical chemistry parameters. The selected findings are presented in Tables 5 and 6 and are discussed below.

For males, there were increases in total protein, albumin, albumin-globulin ratio, γ-GTP, phospholipids and potassium at ≥6,000 ppm; increase in total cholesterol at ≥3,000 ppm; increase in calcium and inorganic phosphorus at 10,000 ppm. There were significant decreases in triglycerides, AST and ALP at ≥3,000 ppm; decrease in CPK at ≥6,000 ppm; decrease in γ-globulin ratio at 10,000 ppm.

Table 4
Selected Hematology Parameters in Rats
Treated with S-41311 for Thirteen Weeks[a]

Parameters	Dosage Levels (ppm)									
	Males					Females				
	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000 4
RBC ($X10^6/\mu l$)	8.5	8.5	8.4	8.3	7.8** (-8)[b]	7.7	7.8	7.7	7.5	6.7** (-13)
HGB (g/dl)	15.1	15.2	14.3** (-5)	14.1** (-7)	13.8** (-9)	14.7	14.8	14.4	13.9** (-5)	12.9** (-12)
HCT (%)	42.3	42.5	39.9** (-6)	39.3** (-7)	38.3** (-9)	40.3	40.7	38.9* (-3)	37.7** (-6)	34.8** (-14)
MCV (fl)	50.1	50.1	47.3** (-6)	47.5** (-5)	49.2	52.8	52.0	50.7* (-4)	50.4** (-5)	52.2
MCH (pg)	17.9	17.9	17.0** (-5)	17.1** (-4)	17.8	19.2	18.9	18.6* (-3)	18.5** (-4)	19.3
MCHC (g/dl)	35.8	35.8	35.9	36.0	36.1	36.5	36.4	36.9	36.7	37.1** (+2)
RET ($X10^4/\mu l$)	19.2	17.5	17.8	21.8	31.9** (+66)	14.6	15.0	17.8* (+22)	20.4** (+40)	30.6** (+110)
RET (%)[c]	2.2	2.0	2.0	2.5	4.0** (+81)	1.8	1.8	2.2	2.6** (+44)	4.4** (+144)
WBC($X10^3/\mu l$)	6.7	7.7	7.7	8.6* (+28)	9.2** (+37)	4.9	4.9	5.4	5.4	5.6
Neut ($X10^3/\mu l$)	0.8	0.9	0.8	0.9	1.1** (+34)	0.5	0.6	0.6	0.6	0.7
Lympho ($X10^3/\mu l$)	5.7	6.6	6.6	7.4* (+30)	7.9** (+38)	4.2	4.2	4.7	4.7	4.8
Baso ($X10^3/\mu l$)	0.01	0.01	0.01	0.01*,[b]	0.02* (+100)	0.00	0.01	0.01	0.01	0.01
PT Time (sec)	16.5	18.4* (+12)	18.1	19.5** (+18)	18.3* (+11)	13.7	13.9	13.9	13.7	13.8
APTT (sec)	21.7	23.2* (+7)	22.7	23.4** (+8)	23.4* (+8)	18.3	18.5	18.3	18.3	18.2
Fib (mg/dl)	241	235	243	237	248	169	167	183* (+9)	179	187** (+11)
PLT (X103/μl)	1156	1154	1255* (+9)	1284** (+11)	1365** (+18)	1112	1108	1239	1219	1327** (+19)

a Extracted from Table 6 (page 108-116) of study no. 200040
b () = % change
c RET (%)= percentage of reticulocytes (number of reticulocytes/total number of blood cells x 100); converted from per thousand to percent by the reviewer
Significantly different from controls; * = $p<0.05$; ** = $p<0.01$

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As shown in table 6, there was an increase in total protein levels as evidenced by an increase in albumin (10%) at ≥6,000 ppm; increase in α2-globulin (≥16%) at ≥3,000 ppm and decrease in γ-globulin (26%) at 10,000 ppm.

For females, there were significant increases in total cholesterol (20%), potassium (7%) and inorganic phosphorus (10%) at 10,000 ppm; increase in direct bilirubin (≥100%) at ≥3,000 ppm and γ-GTP (100%) at ≥6,000 ppm. Decreases were noted in AST (≥19%) and ALT (≥26%) at all dose levels, in plasma cholinesterase (≥35%) at ≥6,000 ppm, and in percent γ-globulin (25%) at 10,000 ppm. Changes in phospholipids at 100 ppm and creatinine at 10,000 ppm were slight and non-dose related.

Table 6. Absolute Values of the Selected Total Protein Fractions in Males[a]

Dose Groups (ppm)	Alb (g/dl)	α2-Glb (g/dl)	γ-Glb (g/dl)
0	3.32	0.32	0.35
100	3.27	0.35	0.39
3,000	3.39	0.37* (+16)	0.35
6,000	3.66** (+10)	0.39** (+22)	0.31
10,000	3.78** (+14)	0.39** (+22)	0.26** (-26)

a Extracted from Text Table A, page 23 of study no.200040
Significantly different from controls;
*=p<0.05;**= p<0.01

F. Urinalysis: No compound-related effects were noted.

G. Sacrifice and Pathology:

1. Organ weight - The organ weight data are summarized in Table 7. The significant increases in absolute

Table 5
Selected Clinical Chemistry Parameters
in Rats Treated with S-41311 for Thirteen Weeks[a]

Parameters	Dosage Levels (ppm)									
	Males					Females				
	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
TG (mg/dl)	53	45	35** (-34)[b]	40* (-25)	40* (-25)	26	20	26	23	28
PL (mg/dl)	78	74	87	103** (+32)	120** (+54)	123	106*	109	109	126
T.Cho (mg/dl)	54	51	67** (+24)	77** (+43)	91** (+69)	70	61	63	68	84** (+20)
T. Bill (mg/dl)	0.11	0.12	0.11	0.11	0.11	0.19	0.17	0.18	0.17	0.17
D.Bill (mg/dl)	0.07	0.07	0.07	0.08	0.08	0.03	0.04	0.06** (+100)	0.08** (+167)	0.07** (+133)
Cre (mg/dl)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6**
K (mEq/l)	4.7	4.6	4.8	5.0* (+6)	5.0** (+6)	4.5	4.5	4.7	4.6	4.8** (+7)
Ca (mg/dl)	9.4	9.3	9.3	9.5	9.6* (+2)	9.8	9.7	9.7	9.8	9.7
IP (mg/dl)	7.6	7.5	7.9	8.0	8.7** (+14)	6.8	6.9	6.8	7.3	7.5* (+10)
ALT (U/l)	37	30	25	23	23	35	26** (-26)	21** (-40)	20** (-43)	17** (-51)
AST (U/l)	108	91	75* (-31)	74** (-31)	63** (-42)	114	92* (-19)	88** (-23)	85** (-25)	75** (-34)
γ-GTP (U/l)	1	1	1	2** (+100)	3** (+200)	1	0	1	2** (+100)	2** (+100)
ALP (U/l)	84	86	67** (-20)	69** (-18)	61** (-27)	43	43	40	39	35
LDH (U/l)	93	82	75	84	73	72	57	66	58	61
CPK (U/l)	82	78	76	69* (-16)	66** (-20)	64	61	61	56	55
Plasma ChE (U/l)	639	613	573	576	568	4507	4441	3880	2920** (-35)	2577** (-43)
TP (g/dl)	6.1	6.1	6.2	6.5** (+7)	6.7** (+10)	6.7	6.5	6.8	6.8	6.7
Alb (%)	54.3	53.4	54.6	56.3* (+4)	56.7** (+4)	61.8	62.2	63.2	62.1	63.6
γ-Glb (%)	5.7	6.3	5.6	4.7	3.9** (-32)	6.8	6.8	6.5	6.2	5.1** (-25)
A/G	1.2	1.2	1.2	1.3* (+8)	1.3** (+8)	1.6	1.7	1.7	1.6	1.8

a Extracted from Table 8 (page 121-128) of study no.200040; b () = % change
Significantly different from controls; * = $p<0.05$; ** = $p<0.01$

and relative organ weights over the control groups were as follows:

Liver: Absolute weights in males and in females at 10,000 ppm; relative weights in both sexes at ≥3,000 ppm.

Kidney: Relative weights in males at ≥3,000 ppm.

Spleen: Absolute weights in females at 10,000 ppm; relative weights in males at 10,000 ppm and in females at ≥6000 ppm.

In addition, increases were also noted in the following: relative heart weights in males at ≥6,000 ppm and in females at 10,000 ppm; relative brain weights in males at ≥6,000 ppm and in females at ≥3,000 ppm; absolute testes weights at 10,000 ppm and relative testes weights at ≥6,000 ppm; and relative thyroid weights in males at 10,000 ppm.

Decreases were noted in the following: Absolute liver weight in females at 100 ppm; absolute kidney weights in females at 100 ppm and ≥6,000 ppm; and absolute brain weight in males at ≥6,000 ppm and in females at 10,000 ppm

The terminal body weights were lower compared to controls in males (83-93% of control) and in females (87-93% of control) at ≥3000 ppm (refer to Table 7).

2. Gross pathology - Compound-related effects observed consisted of dark or blackish spleen in 8/12 males at 10,000 ppm and in 2/12 females at 6,000 ppm as well as in 12/12 females at 10,000 ppm. No treatment-related remarkable findings in other organs were noted in either sex. The selected findings are presented in Table 8.

Table 7
Absolute and Relative Weights of Selected Organs from Rats Treated with S-41311 for Thirteen Weeks[a]

Organ Wts. (g)	Dosage Levels (ppm)									
	Males					Females				
	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
Liver										
A	12.62	11.91	13.24	13.57	14.84**	7.30	6.52**	7.27	7.63	8.35**
R	2.49	2.42	2.80**	3.14**	3.51**	2.53	2.43	2.71**	2.99**	3.31**
Kidneys										
A	3.38	3.26	3.53	3.30	3.20	2.11	1.94**	2.06	1.93**	1.89**
R	0.67	0.66	0.75**	0.76**	0.76**	0.73	0.72	0.77	0.76	0.75
Spleen										
A	0.74	0.70	0.72	0.66	0.75	0.50	0.47	0.50	0.52	0.59**
R	0.15	0.14	0.15	0.15	0.18**	0.17	0.18	0.19	0.21**	0.23**
Heart										
A	1.45	1.40	1.41	1.31	1.38	0.96	0.89	0.88	0.88	0.91
R	0.29	0.29	0.30	0.30*	0.33**	0.33	0.33	0.33	0.35	0.36**
Brain										
A	2.07	2.06	2.03	1.99**	1.97**	1.94	1.91	1.93	1.92	1.86**
R	0.41	0.42	0.43	0.47**	0.47**	0.67	0.71	0.73*	0.76**	0.74**
Thyroid										
A	26	24	25	25	26	23	23	22	21	21
R	5.1	4.8	5.2	5.7	6.2**	7.8	8.4	8.1	8.3	8.3
Testes										
A	3.50	3.45	3.34	3.60	3.70*	--	--	--	--	--
R	0.69	0.71	0.71	0.84**	0.88**	--	--	--	--	--
Terminal Body Weights										
	508	492	472*	434**	424**	289	269*	268*	255**	252**

a Extracted from Tables 9-1 and 9-2 (pages 129-136) of study no. 200040

A= Absolute organ weight; R= Relative organ weight

Statistically significant from controls; * = $p<0.05$; ** = $p<0.01$

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Table 8
Gross Pathological Findings in the Liver and Spleens from Rats Treated with S-41311 for Thirteen Weeks[a]

	Dosage Levels (ppm)									
	Males					Females				
Organs examined	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
Number Examined	12	12	12	12	12	12	12	12	12	12
Liver -										
Enlarged	0	0	0	0	2	0	0	0	0	0
Spleen-										
Enlarged	0	0	0	0	1	0	0	0	0	1
Black	0	0	0	0	8	0	0	0	2	12

a Extracted from Table 10, pages 137 and 138 of study no. 200040

3. Microscopic pathology - No neoplastic lesions were observed in treated animals. Compound-related non-neoplastic lesions were found during histopathological evaluation of the liver, spleen, kidney and salivary glands. These are presented in Table 9. Liver hypertrophy (≥6,000 ppm), along with a few eosinophilic hepatocytes, and presence of hemosiderin pigment, was observed in males and females at 10,000 ppm. Decrease in hepatocellular vacuolation was noted in both sexes at ≥3,000 ppm. The changes in spleen observed in both sexes consisted of an increase in extramedullary hematopoiesis in males at ≥6,000 ppm and an increase in hemosiderin pigment in males at ≥6,000 ppm as well as in females at ≥3000 ppm. A small amount of yellowish-brown pigment, as detected by staining, was observed in the kidneys of both sexes at 6,000 and 10,000 ppm. Treatment-related changes in the salivary glands observed in both sexes consisted of swelling of acinar cells (at ≥3,000 ppm) and edema (at 6,000 and 10,000 ppm) of submandibular glands.

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Table 9
Histopathological Findings in Liver, Spleen, Salivary glands, and Kidneys from Rats Treated with S-41311 for Thirteen Weeks[a]

	Dosage Levels (ppm)									
	Males					Females				
	0	100	3,000	6,000	10,000	0	100	3,000	6,000	10,000
Number Examined	12	12	12	12	12	12	12	12	12	12
Liver -										
Hypertrophy	0	0	0	2 (17)	9 (75)	0	0	0	0	7 (58)
Vacuolation	11	11	7	7	2	11	10	7	4	3
Eosinophilic hepatocytes	0	0	0	1	8 (67)	0	0	0	0	5 (42)
Hemosiderin pigment	0	0	0	0	2 (17)	0	0	0	1	2 (17)
Bile duct hyperplasia	7	6	11	7	8	7	9	10	8	7
Spleen-										
Increased extramedullary hematopoiesis	0	0	0	5 (42)	11 (92)	0	0	0	3	8 (67)
Hemosiderin pigment	0	0	0	4 (33)	9 (75)	0	0	2 (17)	5 (42)	10 (83)
Salivary gland-										
Swelling of acinar cells in submandibular gland	0	0	5	7 (58)	11 (92)	0	0	1	6 (50)	8 (67)
Edema in submandibular gland	0	0	0	4 (33)	6 (50)	0	0	0	4 (33)	4 (33)
Kidneys-										
Yellowish-brown pigment	0	0	0	3 (25)	10 (83)	0	0	0	1	2

a Extracted from Table 11 (pages 139-147) of study no.200040
( ) = percent

IV. DISCUSSION

A. Reviewer's interpretation of study results: The analytical chemistry data indicate that the purity, stability and homogeneity of S-41311 were within acceptable limits and the animals received appropriate dosages of the test compound.

Dietary administration of S-41311 failed to produce adverse effects on the survival, clinical signs, and ophthalmology. The evaluation of body weight and body weight gain data indicated that the body weight gain was lower compared to controls in males (≥78% of control) and in females ≥83% of control) at ≥3,000 ppm over the entire treatment period. These changes were accompanied by decreases in food consumption (g/rat/day) and food efficiency (g/kg/day) during the first week of the treatment period.

A compound-related hemolytic anemia was noted in both sexes at ≥3,000 ppm as evidenced by decreases in hematocrit, hemoglobin and erythrocyte counts accompanied by an increase in hemosiderin pigment in the liver (10,000 ppm) and spleen. There was no increase in indirect bilirubin at the above dose levels. This suggests that the anemia was only mild in nature. Because of a lack of significant changes in erythroblast count and M/E ratio, as well as absence of histopathological findings in bone marrow examination, no obvious effect on the hematopoietic system was observed. Increase in plasma potassium was associated with anemia as erythrocytes also contained significant amounts of potassium. Increases in reticulocyte count, percentage of reticulocytes, spleen weight, enlarged and black spleen, and increased extramedullary hematopoiesis in the spleen along with increases in leukocyte count, lymphocytes and neutrophils (males) were considered to be compensatory responses to anemia.

Compound-related interference with liver functioning was observed in both sexes (10,000 ppm) as shown by hepatocellular hypertrophy, and the presence of eosinophilic hepatocytes. These changes were considered to be adaptive in nature as they were not accompanied by severe changes in liver histopathology such as necrosis or hepatocellular degeneration. Increased relative liver weights in males and females (10,000 ppm) were secondary to a decrease in body weight gain.

Decreases in AST, ALT, ALP and CPK (one or more dose groups) levels were not biologically significant. Although there were increases in direct bilirubin (≥3,000 ppm; females) and γ-GTP (≥6,000 ppm; both sexes), they were not associated with changes in the histopathology of the bile duct. Therefore, the toxicological significance of these findings

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is unclear. A slight decrease in hepatocellular vacuolation, commonly induced by pyrethroid insecticides, was observed at all dose levels. Interference in protein and lipid metabolism in the liver of males was indicated by increases in albumin, α2-globulin and phospholipids, and decreases in total cholesterol (≥3,000 ppm), γ-globulin (≥6,000 ppm), and triglycerides (≥3,000 ppm).

The additional changes such as microscopic alterations in the kidney and submandibular salivary glands, and increases in organs weights such as heart, testes and thyroid, were not accompanied by other changes such as salivation, or changes in kidney function as revealed by biochemical parameters in the blood and urine examinations, or histopathological changes in heart, testes and thyroid. Increases in relative organ weights were secondary to a decrease in body weight gain and, therefore, they were not considered to be biologically significant.

The LOEL in both sexes was 3,000 ppm (178.6 and 196.6 mg/kg/day, for males and females, respectively), based on decreased body weight gain and food consumption, and hemolytic anemia; the NOEL is 100 ppm (5.9 and 6.7 mg/kg/day in males and females, respectively).

B. Study deficiencies: The following deficiencies were noted:

- Two rats were maintained in each cage.
- Food consumption was determined per cage rather than per animal.

However, the above deficiencies did not adversely impact upom the outcome of the study results.

Imiprothrin Developmental Toxicity (83-3b)

Reviewed by: Sanjivani B.Diwan, Ph.D. Sanjivani B. Diwan Date: 7/31/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson, Date: 7/31/96
Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - *[Rabbit]*; OPPTS 870.3700 [§83-3b]

DP BARCODE: D222183 SUBMISSION CODE: S498997
P.C. CODE: 004006 TOX. CHEM. NO.: [New Chemical]
MRID NO.: 43750731; 43750733

TEST MATERIAL (PURITY): S-41311 (≥92.2%)

SYNONYMS: Imiprothrin

CAS NO.: Not available

STUDY REPORT NUMBERS: Study No. 2361; 2595
Reference No. SGT-20-0025; SGT-30-0058

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan

TESTING FACILITY: Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd., Osaka, Japan.

TITLE OF REPORT: Study on Oral Administration of S-41311 During the Period of Fetal Organogenesis in Rabbits.

AUTHOR: S. Kawamura

REPORTS ISSUED: May 14, 1992; December 28, 1992

EXECUTIVE SUMMARY:

The developmental toxicity of S-41311 (≥92.2% a.i.) in JW-NIBS rabbits was investigated in two phases.

During phase I (initial study; MRID# 43750731), S-41311 was administered by gavage to pregnant rabbits (10/dose) at dose levels of 0, 30, 100 and 300 mg/kg/day from gestational days (GD) 6 to 18, inclusive.

The maternal LOEL was 100 mg/kg/day based on decrease in body weight gain (80%) and food consumption (23%). At 300 mg/kg/day, pale urine was noted in all animals; additionally, increased mortality (2/17) and premature labor (5/17) resulting in abortion were also noted. The maternal NOEL was 30 mg/kg/day.

In this study, lower mean fetal body weights, fusion of nasal bones and hypoplasia of the frontal bone were noted at ≥100 mg/kg/day. A dose-dependent increase in the incidence of 27th pre-sacrococcygeal vertebra was noted in all treated groups compared to controls. At 30 mg/kg/day, the incidence of this anomaly was slightly above the incidence in concurrent and historical controls and, therefore, its causal relationship with the test substance could not be determined. Although the NOEL for developmental toxicity was <100 mg/kg/day, the actual NOEL could not be established.

The phase II (additional study; MRID# 43750733) was therefore, conducted to establish the NOEL for developmental toxicity. During this phase, S-41311 was administered by gavage to groups of pregnant rabbits (20/group) at dose levels of 0, 3, 10, or 30 mg/kg/day from GD 6–18, inclusive.

No maternal toxicity was observed. Therefore, the NOEL for maternal toxicity was 30 mg/kg/day. Contrary to the findings in phase II of the study, there was no compound-related increase in the incidence 27th presacral vertebrae at 30 mg/kg/day when analyzed on a litter basis. Therefore, the increased incidence observed in phase II of the study was considered to be incidental. The NOEL for developmental toxicity was 30 mg/kg/day.

The combined results of the two phases of the study established the following:

The maternal LOEL is 100 mg/kg/day, based on decrease in body weight gain and food consumption. In addition, pale urine, increased mortality, and premature delivery resulting in abortion were observed at 300 mg/kg/day. The maternal NOEL is 30 mg/kg/day.

The developmental LOEL is 100 mg/kg/day, based on the findings of lower mean fetal body weights, fusion of nasal bones, hypoplasia of the frontal bone and increased incidence of 27th pre-sacral vertebrae. Developmental toxicity NOEL is 30 mg/kg/day.

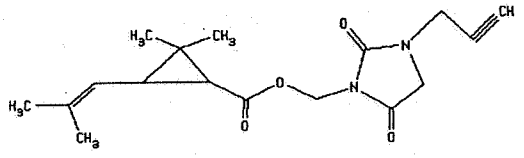
This study is classified as Acceptable and satisfies the guideline requirement for a developmental toxicity study (§83-3b) in rabbits.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: S-41311
   Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
   Synonym: Imiprothrin
   Description: A clear, yellow-orange oily liquid (MRID # 43750730
   Lot #: Y-011001
   Purity: 92.9% Phase I; 92.2% Phase II
   Stability of compound: Test suspension in corn oil was stable at room temperature for 14 days
   Structure:



2. Vehicle: Corn oil (Nacalai Tesque, Co., Ltd.)

3. Test animals: Rabbit
   Strain: JW-NIBS
   Age and weight at study initiation: Males-6 months; Females - 5 months;
   Phase I- Males - 2.87 to 3.17 kg; Females - 2.56 to 3.17 kg
   Phase II- Males - 2.74 to 3.24 kg; Females - 2.41 to 3.08 kg
   Source: Nissei-Ken Co., Ltd., Japan
   Housing: Individually in aluminum cages
   Diet: Rabbit pellet diet (NRT-1, Nissei-Ken Co., Ltd. Japan) ad libitum
   Water: Tap water ad libitum
   Environmental conditions: Temperature: $22 \pm 2^{0}C$
   Relative Humidity: $55 \pm 10\%$
   Air changes: 10/hour
   Photoperiod: 12 hours light/dark
   Acclimation period: 2 weeks

B. PROCEDURES AND STUDY DESIGN:

1. Insemination:

   Pooled semen sample was diluted 10-fold with saline. Females were artificially inseminated with 0.5 mL of the mixture of sperm from untreated male rabbits. However, the concentration of spermatozoa/0.5 mL saline was not specified. Immediately after insemination, each doe

mL saline was not specified. Immediately after insemination, each doe was injected intravenously with 50 IU of chorionic gonadotrophin (Sankyo Zoki Co., Ltd.). The day of insemination was designated day 0 of gestation.

2. Animal Assignment:

Following a period of acclimation, the rats were assigned to study groups via a body weight-dependant randomization scheme (Table 1).

Table 1. Animal Assignment

Dose Group	Phase I		Phase II	
	Dose in mg/kg/day or Concen. (w/v %)	Number Assigned	Dose in mg/kg/day or Concen. (w/v%)	Number Assigned
Control	0	17	0	20
Low	30 (6)	15	3 (0.6)	20
Mid	100 (20)	15	10 (2.0)	20
High	300 (60)	17	30 (6.0)	20

3. Dose Level Selection Rationale

The dose levels were selected on the basis of the results of a dose-range-finding study (Study #2292; Report No. SGT-10-0002; MRID# 43750732; June 13, 1991). In this study S-41311 (92.9%; Lot # Y-011001) was administered to non-pregnant JW-NIBS rabbits at dose levels of 30, 100 and 300 mg/kg/day for two weeks. Prior to death, tremors, salivation or lacrimation were noted in 2 rabbits receiving 100 mg/kg/day and one rabbit receiving 300 mg/kg/day. Pale urine was observed in all rabbits receiving 300 mg/kg/day. However, author considered these findings to be incidental. Decreased food consumption (78% of controls) was noted at 300 mg/kg/day on day 5 of treatment. Based on this finding, 300 mg/kg/day was chosen as the highest dose for the developmental toxicity study.

4. Dosing

The dosing solutions were prepared once in corn oil. The dosing solution was administered at a volume of 0.5 ml/kg b.w. from Day 6 through 18 of gestation. The doses for individual animals were calculated based on the body weight on day 6 of dosing. The control group received corn oil. The concentration analysis was performed. The

dosing solutions were stable at room temperature for 14 days. The homogeneous distribution of the material was achieved by mixing. The 300 mg/kg/day dosing solution was warmed at 40°C and stirred before administration.

C. OBSERVATIONS:

1. Maternal Observations and Evaluations - The animals were checked daily for signs of toxicity and mortality. Body weights and food consumption were recorded on gestation days (GDs) 0 (body weight measurements only), 6, 9, 12, 15, 18, 22, 25 and 28. Does were sacrificed by intravenous injection of pentobarbital on day 28 of gestation. Examinations at sacrifice consisted of:

   - Gross pathology observations of the organs in the thoracic and/or abdominal and pelvic regions were made; gall bladder was processed for histopathology.

   - Number of corpora lutea

   - Number of implantations

   - Numbers of resorptions (early and late) and live and dead fetuses

   - Number and distribution of fetuses in each uterine horn

2. Fetal Evaluations - The fetuses were examined in the following manner:

   - Individual fetal weight and sex

   - External anomalies

   - Visceral anomalies by dissecting the thoracic cavity and abdomen of all the fetuses following fixing in alcohol; fetal heart, kidney, and eye balls were fixed in Bouin's fixative and examined to assess the internal structure.

   - Skeletal anomalies for the fetuses were examined as follows: For phase I, specimens in alcohol were stained with Alizarin S using method of Kawamura et al. (1990). For Phase II the fetuses were fixed in 99% ethanol and stained with alizarin blue, alcian blue and acetic acid; fetuses were then cleared in 1.5% potassium hydroxide and treated with 20% glycerine prior to skeletal examination .

3. Historical control - Data were provided to allow comparison with concurrent controls.

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D. DATA ANALYSIS

1. STATISTICAL ANALYSIS: For phase I of the study, the data on nonpregnant does and doe # 308 (time of abortion unknown) were excluded from analyses. For phase II, data for 2 does (# 312, 313) from the 100 mg/kg group and one doe (#412) from the 300 mg/kg groups were excluded for analyses from the time of gavage error. In addition, data on 4 does that had abortions were excluded from further analysis. The following methods were used.

- Maternal body weight and body weight change, number of corpora lutea, implantations, and live fetuses, mean fetal body weight/litter, the incidence of number of ossified sacrococcygeal vertebral bodies and proximal as well as middle phalanges of the finger on a litter basis-- Student's t-test and Aspin-Welch's test for homogeneous variances and F-test for heterogeneous variances

- Maternal mortality, incidence of pregnancy and number of litters with fetal findings -- Fisher's Exact test

- Incidence of implantation, embryofetal mortality, sex ratio, fetal findings (incidence of malformations, variations, retardations;percentage of fetuses with tarsus, unossified fifth and/or sixth sternebrae,unossified metacarpal of the first finger of forelimb and middle phalanges of the fifth toe of the hindlimb -- Mann-Whitney's U-test

When significant intergroup differences were present (by One-Way Analysis of Variance), then least-significant-difference test was used for group comparison.

II. RESULTS

A. TEST MATERIAL ANALYSES

The concentration analysis for the dosing solutions taken during both phases of the study indicated values within 8% of the target (Phase I, range: 93.0%-94%; Phase II, range: 93.0%-100.0% of the nominal concentration). The test compound was homogeneously distributed in the dosing suspension. The stability analysis of the dosing solutions performed earlier during the range-finding study revealed values within 10% of the target (range: 91%-107%) and indicated that the compound was stable in corn oil for up to 14 days.

B. MATERNAL TOXICITY

1. Mortality -Treatment-related mortality/moribundity and abortions were noted at 300 mg/kg/day.

During phase I of the study, one doe (#403) from the 300 mg/kg group died on Day 26 of gestation. Another doe (#414) was found moribund on Day 18 of gestation; this animal had bradypnea in the prone position. Premature labor resulting in abortions were noted in one doe each from the control (#109), 100 mg/kg/day (#308) and 300 mg/kg/day (#401) dose groups on Days 25, 27, and 20 of gestation, respectively. Four additional does from the 300 mg/kg dose group were confirmed of having undergone abortion or premature labor upon cesarean section (# 402, 410, and 417) or at necropsy (#403).

During phase II of the study, premature labor resulting in abortion was noted in one doe each from 10 mg/kg/day (doe # 308) and 3 mg/kg/day (doe #215) dose groups on gestation days 28 and 27, respectively. One doe (#204) from 3 mg/kg/day group exhibited tremor immediately following dosing and died few minutes later; upon necropsy the cause of death was attributed to gavage error.

2. Clinical observations - Treatment-related change in the color of urine was observed at 300 mg/kg/day.

During phase I of the study, pale red urine was noted in all animals from the 300 mg/kg dose group from Day 6 through 12 of gestation. Some of the clinical signs were caused due to gavage error and are discussed below. Immediately following dosing, tremor was noted in one animal (#412) at 300 mg/kg on Day 17 of gestation and in one animal (#312) at 100 mg/kg on Day 8 of gestation. Animal # 312 had mydriasis and abnormal respiratory sound and died in 30 minutes. One animal (#313) at 100 mg/kg/day vomited red fluid.

No treatment-related clinical signs of systemic toxicity were noted during phase II of the study.

3. Body weight - Body weight gain data are summarized in Table 2. Compound-related changes in body weight and body weight gain were observed at $\geq$100 mg/kg/day.

During phase I, the body weights of animals (data not shown) at $\geq$100 mg/kg/day were lower compared to controls throughout the dosing period. The body weights at 30 mg/kg/day were comparable to controls.

At 300 mg/kg/day, the mean body weight gain was lower (loss of 0.27

g vs gain of 0.10 g in controls) throughout the treatment period (GD 6-18) and remained lower until sacrifice (an overall decrease of 73% compared to controls during GD 6-28). At 100 mg/kg/day, the body weight gain tended to decrease compared to controls (80% during GD 6-18; 23% during GD 6-28) and at 30 mg/kg/day, it was comparable to controls. Because of lack of data on uterine weights, the corrected body weight gain could not be determined.

During phase II, the body weights and body weight gain data of treated and control groups were comparable throughout the treatment-and post-treatment periods.

4. Food consumption - Food consumption data are summarized in Table 3. Compound-related decreases in food consumption were noted at ≥100 mg/kg/day.

During phase I and throughout the entire treatment-period (GD 6–18), compound-related decreases in mean food consumption were observed at 300 mg/kg/day (76%; $p<0.01$) and at 100 mg/kg/day (23%; non-significant) compared to controls. A compensatory increase in food consumption was noted during the post-dosing period at ≥100 mg/kg/day.

During phase II, the food consumption was comparable among the treated and control groups throughout the treatment- and post-treatment periods.

5. Necropsy Findings - No compound-related findings were noted.

During phase I at cesarean section, three dams at 300 mg/kg/day had mazolysis indicating that they had abortions or premature labor. Necropsy of these animals revealed blackish points or depression on gastric or duodenal mucosa, gas filled GI tract, muddy contents in cecum, yellowish points on gall bladder mucosa and pale color of heart and kidney. Although these findings appeared to be compound-related, histopathology revealed no treatment-related abnormalities.

During phase II of the study, incidental findings noted on the liver lobes included whitish points in 3 dams at 30 mg/kg/day, whitish spot in one dam at 3 mg/kg/day, and blackish point in one control dam. Additional findings noted in one more dose groups included whitish spot and scar on the kidney, blackish points on gastric or duodenal mucosa, deformed spleen abnormalities of gall bladder. These occurred at a low frequency and were considered to be unrelated related to treatment.

TABLE 2. Mean Body Weight Gain (g ± S.D.)

Dose Group in mg/kg/day	Dosing Period (GD 6-18)	Post-Dosing Periods (GD 18-28)	Dosing and Post-dosing Periods (GD 6-28)[b]
Phase I[a]:			
0 (13)[c]	0.10 ± 0.08	0.22 ± 0.10	0.22 ± 0.10 (12)[d]
30 (11)	0.13 ± 0.07	0.28 ± 0.14	0.29 ± 0.13 (11)
100 (11)	0.02 ± 0.16	0.17 ± 0.11	0.17 ± 0.10 (10)
300 (10)	-0.27 ± 0.23**	0.07 ± 0.10**	0.06 ± 0.09 (8)
Phase II[e]:			
0 (17)	0.08 ± 0.08	0.15 ± 0.10	0.14 ± 0.09 (17)
3 (17)	0.11 ± 0.06	0.20 ± 0.12	0.20 ± 0.11 (17)
10 (18)	0.09 ± 0.07	0.18 ± 0.10	0.17 ± 0.10 (18)
30 (20)	0.11 ± 0.07	0.22 ± 0.11	0.21 ± 0.10 (20)

[a]Data were extracted from Study No. 200025, Table 4, p. 44 and Appendix 2-1 to 2-4, p. 82-85
[b]Calculated by the reviewer
[c]Number of dams in each group at the start of dosing
[d]Number of dams in each group at study termination
[e]Data were extracted from Study No. 300058, Table 4, p. 34 and Appendix 3-1 to 3-4, p. 70-73

TABLE 3. Mean Food Consumption (g/animal/day ± S.D.)

Dose Group in mg/kg/day	Dosing Period (GD 6)	Dosing Period (GD 18)	Post-dosing Period (GD 28)
Phase I[a]:			
0 (13)[b]	157 ± 28.4	140 ± 52.0	127 ± 29.0 (12)[c]
30 (11)	155 ± 27.1	149 ± 22.0	134 ± 25.0 (11)
100 (13)	176 ± 21.4	108 ± 68.3	137 ± 21.2 (10)
300 (11)	166 ± 16.0	34 ± 48.0**	142 ± 26.0 (8)
Phase II[d]:			
0 (17)	167 ± 26.0	140 ± 48.0	115 ± 26.0 (17)
3 (17)	176 ± 22.4	151 ± 33.3	122 ± 31.0 (17)
10 (18)	165 ± 24.4	139 ± 38.0	112 ± 28.0 (18)
30 (20)	168 ± 24.1	143 ± 37.1	127 ± 29.2 (20)

[a]Data were extracted from Study No. 200025, Table 5 and page 45
[b]Number of dams in each group at the start of dosing
[c]Number of dams in each group at study termination
[d]Data were extracted from Study No. 300058, Table 5 and page 35

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6. Cesarean section Data - Data are summarized in Table 4A and 4B. Compound-related decreases in fetal body weights were noted at ≥100 mg/kg/day.

   During phase I of the study, the fetal body weights decreased at ≥100 mg/kg/day compared to controls. Although the incidence of abortions was higher at these dose levels, there were no compound-related and/or statistically significant differences in the surviving does in conception rate, in the mean number of corpora lutea and implantations or incidences of pre- and post-implantation losses, the number of resorptions and viable fetuses.

   No compound-related effects were observed in any dose groups during phase II of the study.

   For both phases of the study, the sex distribution of the fetuses and mean fetal weights in all test groups were comparable with the controls.

C. DEVELOPMENTAL TOXICITY

A summary of fetal external, visceral, and skeletal observations is provided in Table 5A and 5B. During both phases of the study, no compound-related increases in the fetal/litter incidences of external, visceral, and skeletal malformations were noted.

The incidences of selected skeletal fetal findings are presented in Tables 6A and 6B. These included minor anomalies and variations. Compound-related increases in minor fetal skeletal anomalies (hypoplasia of the frontal bone and fusion of nasal bone [300 mg/kg/day]) and variation (27th pre-sacral vertebrae) were noted at ≥100 mg/kg/day.

1. External observations - No compound-related malformations were noted.

   During phase I, there were no fetuses with external abnormal findings in any dose groups including controls.

   During phase II, flexed contracture of the wrist joint was noted in one fetus at 30 mg/kg/day; one fetus at 3 mg/kg/day had microphthalmia (Table 6B). These findings are commonly seen in this strain of rabbit and were not considered to be compound-related. No variations were observed.

2. Visceral observations - No compound-related visceral malformations or variations were noted.

TABLE 4A. Cesarean Section Observations for Phase I Study[a]

Parameter	Dose Level (mg/kg/day) 0	30	100	300
No. animals assigned	17	15	15	17
No. animals inseminated	17	15	15	17
No. animals pregnant	15	11	13	17
Pregnancy rate (%)	88	73	87	100
No. animals excluded[b]	2	0	2	3
No. animals aborted	1	0	1	5
No. animals dead/ moribund[c]	0	0	0	2
Total corpora lutea	109 (12)[d]	103 (11)	100 (10)	85 (8)
Corpora lutea/dam	9.1 ± 1.9[e]	9.4 ± 2.1	10.0 ± 2.2	10.6 ± 1.3
Total implantations	86 (12)	81 (11)	82 (10)	70 (8)
Implantations/dam	7.2 ± 2.3	7.4 ± 2.8	8.2 ± 2.0	8.8 ± 2.3
Total live fetuses	74 (12)	75 (11)	70 (10)	64 (8)
Live fetuses/dam	6.2 ± 2.3	6.8 ± 2.8	7.0 ± 1.6	8.0 ± 2.1
Total resorptions	12	6	12	6
Early	10	4	7	4
Late	2	2	5	2
Resorptions/dam	0.9 ± 0.9	0.5 ± 0.5	1.2 ± 1.0	0.8 ± 0.7
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Fetal weight/litter (g)				
-male fetuses	37.3 ± 3.7	37.8 ± 4.5	35.7 ± 3.8	31.7 ± 4.0**
-female fetuses	36.4 ± 4.3	37.2 ± 6.4	34.6 ± 6.4	30.6 ± 3.3**
Preimplantation loss (%)	21.1	21.4	18.0	17.6
Postimplantation loss(%)	14.0	7.4	14.6	8.6
Sex ratio (% male)	47	45	46	42

[a]Data were extracted from Study No. 200025, Tables 1 and 11, p. 40, 51; Appendix 6-1 to 6-4, p. 100-103.
[b]Excluded prior to or during dosing from further analysis.
[c]Includes doe that aborted litter.
[d]Number of does included in the analyses
[e]Mean ± S.D.

TABLE 4B. Cesarean Section Observations for Phase II Study[a]

Parameter	Dose Level (mg/kg/day) 0	3	10	30
No. animals assigned	20	20	20	20
No. animals inseminated	20	20	20	20
No. animals pregnant	17	19	19	20
Pregnancy rate (%)	85	95	95	100
No. animals excluded[b]	0	1	0	0
No. animals aborted	0	1	1	0
No. animals dead/ moribund[b]	0	1	0	0
Total corpora lutea	162 (17)[c]	173 (17)	171 (18)	185 (20)
Corpora lutea/dam	9.5 ± 1.9[d]	10.2 ± 2.0	9.5 ± 1.9	9.3 ± 1.7
Total implantations	125 (17)	136 (17)	139 (18)	143 (20)
Implantations/dam	7.4 ± 1.8	8.0 ± 2.5	7.7 ± 2.2	7.2 ± 2.4
Total live fetuses	113 (17)	116 (17)	127 (18)	126 (20)
Live fetuses/dam	6.6 ± 2.1	6.8 ± 2.5	7.1 ± 2.2	6.3 ± 2.5
Total resorptions	12	20	12	17
Early	10	14	9	14
Late	2	6	3	3
Resorptions/dam	0.7 ± 0.8	1.2 ± 1.3	0.7 ± 0.8	0.9 ± 0.9
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Fetal weight/litter (g)				
-male fetuses	35.7 ± 4.2	35.7 ± 3.4	35.1 ± 3.5	38.3 ± 4.6
-female fetuses	34.4 ± 3.7	34.2 ± 3.5	34.5 ± 2.9	36.8 ± 5.4
Preimplantation loss (%)	22.8	21.4	18.7	22.7
Postimplantation loss(%)	9.6	14.7	8.6	12.0
Sex ratio (% male)	54	57	52	57

[a]Data were extracted from Study No. 300058, Tables 1, 2 and 7, p. 30, 31, 37; Appendix 6-1 to 6-4, p. 86-89.
[b]Excluded from analysis; death due to gavage error
[c]Number of does included in the analyses
[d]Mean ± S.D.

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TABLE 5A. Summary of Fetal External, Visceral, and Skeletal Malformations[a] - Phase I

Findings	Dose Level (mg/kg/day) 0	30	100	300
No. fetuses (litters) examined	74 (12)	75 (11)	70 (10)	64 (8)
External:				
No. fetuses (litters) with malformations	0	0	0	0
Visceral:				
No. fetuses (litters) with variations	2 (2)	1	1	2 (2)
- Heart				
Ventricular septal defect	1	0	0	0
Hypoplastic right ventricle	0	0	0	1
- Hypoplasia of ovary	1	0	0	0
- Absence of left cranial vena cava	0	1	1	1
Skeletal:				
No. fetuses (litters) with variations	0	0	0	0

[a]Data were extracted from Study No. 200025, Tables 13, 14 and 19, p. 53, 54, 65, 66; Appendix 13-1 to 13-4, p. 128-131.
[b]More than one type of anomaly may be found in one fetus.

TABLE 5B. Summary of Fetal External, Visceral, and Skeletal Malformations[a] - Phase II

Findings	Dose Level (mg/kg/day) 0	3	10	30
No. fetuses (litters) examined	113 (17)	116 (17)	127 (18)	126 (20)
External:				
No. fetuses (litters) with malformations	0	1	0	1
- Flexion contracture of the wrist joint	0	0	0	1
- Microphthalmia	0	1	0	0
Visceral:				
No. fetuses (litters) with malformations	0	0	0	0
Skeletal:				
No. fetuses (litters) examined	113 (17)	116 (17)	127 (18)	126 (20)
No. fetuses (litters) with malformations	0	0	1	0
- Cervical vertebral arch asymmetry of vertebral arch	0	0	1	0

[a]Data were extracted from Study No. 300058, Tables 8 and 9, p. 38-39; Appendix 7-2 to 7-4 and 8-3, p. 91-93 and 96.
[b]More than one type of anomaly may be found in one fetus.

TABLE 6B. Summary of Selected Fetal Skeletal Observations[a]- Phase II

Findings[b]	Dose Level (mg/kg/day) 0	3	10	30
No. fetuses (litters) examined	113 (17)	115 (17)	127 (18)	125 (20)
Minor Anomalies:				
No. fetuses (litters) with anomalies	18 (11)	30 (13)	23 (13)	18 (10)
- Cervical vertebra fused arch and body	15 (11)	24 (12)	19 (11)	16 (8)
- Absence of body of hyoid bone	1	1	0	0
Variations:				
No. fetuses (litters) with variations	31 (13)	32 (15)	31 (12)	40 (15)
- Cervical vertebral body deformity	0	0	5 (5)*	1
- Body of Hyoid bone separation	22 (10)	20 (11)	16 (7)	27 (12)
- 27th presacral vertebra	2 (2)	6 (4)	5 (4)	6 (5)
- 13th rib	8 (5)	8 (8)	4 (3)	5 (4)

[a]Data were extracted from Study No. 300058, Table 10 and 11, p. 42-52; Appendices 9-1 to 9-4 and 10-1 to 10-4, p. 98-105.
[b]More than one type of anomaly may be found in one fetus.
* p =<0.05

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TABLE 6A. Summary of Selected Fetal Skeletal Observations[a]- Phase I

Findings[b]	Dose Level (mg/kg/day) 0	30	100	300
No. fetuses (litters) examined	74 (12)	75 (11)	70 (10)	64 (8)
Minor Anomalies:				
No. fetuses (litters) with anomalies	15 (7)	12 (6)	11 (3)	30 (7)
- Nasal bone fusion	1	0	1	9 (4)*
- Frontal bone-hypoplasia	0	0	2 (1)	10 (2)
- Cervical vertebrae fused arch and body	13 (7)	11 (6)	8 (3)	17 (6)
Variations:				
No. fetuses (litters) with variations	29 (11)	33 (10)	33 (10)	29 (7)
- Body of hyoid bone separation	16 (8)	27 (9)	20 (8)	20 (6)
- 27th presacral vertebra	1	6 (4)	7 (3)	11 (3)
- 13th rib	6 (2)	7 (4)	7 (4)	8 (3)

[a]Data were extracted from Study No. 200025, Tables 15 and 16, p. 55-62; Appendices 9-1 to 9-4 and 10-1 to 10-4, p. 112-119.
[b]More than one type of anomaly may be found in one fetus; data for doe #312 was excluded from analysis due to gavage error on GD 8.
* $p \leq 0.05$

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IV.b

During phase I, visceral malformations were noted in all dose groups (Table 6A). These included ventricular septal defect and hypoplasia of ovary in two control fetuses from two separate litters; hypoplasia of right ventricle in one fetus at 300 mg/kg/day, and defect of left anterior vena cava in one fetus each at 30, 100 and 300 mg/kg/day.

Minor visceral anomalies (data not shown) were found in all dose groups. These included small raised area in small intestine in 2, 1, and 1 fetuses in the control, 30, and 100 mg/kg/day groups, respectively; bifurcation of appendix in one fetus each in the control and 100 mg/kg/day groups; deformed gall bladder in one fetus each in the control and 300 mg/kg/day groups; persistent left azygous vein and deformed bile duct in one fetus each in the 300 mg/kg/day group.

Visceral variations (data not shown) were noted in all dose groups. These consisted of abnormal lobulation of lung, supernumerary coronary orifice in heart and abnormal course of caudal vena cava and subclavian artery. Because of lack of dose-response, they were considered to be unrelated to the treatment.

No visceral malformations, minor anomalies or variation were seen during phase II of the study.

3. Skeletal Observations - No compound-related skeletal malformations were seen during both phases of the study. However, compound-related increases in the incidence of minor anomalies and variations were observed at $\geq$100 mg/kg/day.

Malformations: During phase I, no skeletal malformations were noted in any dose groups. During phase II of the study, the only skeletal malformation seen was asymmetry of the cervical vertebral arch in one fetus at 10 mg/kg/day.

Minor anomalies: The minor anomalies noted during phase I included fusion of nasal bone in one fetus each in the control and 100 mg/kg/day groups. Nine fetuses in 4 litters at 300 mg/kg/day had this anomaly and the incidence was significantly higher compared to controls. There was tendency towards increased incidence of hypoplasia of the frontal bone as noted in one male and one female fetus from the same litter at 100 mg/kg/day and 10 fetuses in 5 litters at 300 mg/kg/day. These fetuses also had lower body weights. This finding was not seen in controls (Table 6A).

Other minor anomalies that occurred without a clear dose-response in the control and 300 mg/kg/day included fusion of cervical vertebral body and arch, incomplete ossification of nasal or frontal bone, absence of

body of hyoid bone, fusion of sternal ossification center and asymmetry of sternal ossification center; these were not considered to be treatment-related. These anomalies were found at a comparable frequency in the concurrent controls.

During phase II, the minor anomalies noted in one or more dose groups included fusion of cervical vertebral body and arch and, separation of frontal bone, separation of parietal bone, incomplete ossification of the parietal bone, absence of the body of hyoid bone, fusion of sternebrae, and absence of digital extremities. The incidences of these findings were comparable to controls.

Variations: During phase I, increase in the incidence of skeletal variation such as 27 pre-sacral vertebra was noted in all dose groups compared to controls. The incidence of this variation was 1, 6(4), 7(3), and 11(3) fetuses (litters) in the control, 30, 100, and 300 mg/kg/day dose groups, respectively (Table 6A). In all dose groups, the incidence increased on a litter basis in a dose-related manner (1.5, 2.3 and 3.6 fetuses/litter at 0, 30, 100 and 300 mg/kg/day, respectively) as well as exceeded that of concurrent controls (1.0 fetus/litter).

During phase II, the incidence of 27 pre-sacral vertebrae was higher in all dose groups compared to controls (2 (2), 6(4), 5(5), and 6(5) fetuses (litters) at 0, 3, 10, and 30 mg/kg/day, respectively; Table 6B) and exceeded that of historical controls (1[1]). However, the increase in the incidence of this variation, on a fetal/litter basis, occurred in a non-dose-related manner (1.0, 1.5, 1.0 and 1.2 fetuses/litter at 0, 3, 10, and 30 mg/kg/day, respectively).

Based on these findings, the LOEL for developmental toxicity was established at 100 mg/kg/day; the NOEL was 30 mg/kg/day.

Other variations observed during both phases of the study, in one or more dose groups, included separation of hyoid bone, flexure of hyoid arch, cervical rib, separation of cervical vertebral body, cervical rib, separation of sternebra, separation of sternal ossification center, lumbarization of sacral vertebra, deformation and displacement of sacrococcygeal bodies and 13th ribs. The incidences of these finding were not different from that of the control group. Therefore, these findings were not considered to be treatment-related.

III. DISCUSSION:

A. MATERNAL TOXICITY: Compound-related toxicity was observed in maternal animals during the treatment period at 100 mg/kg/day. It was manifested as mortality, abortions and decrease in body weight gain and food consumption

mortality, abortions and decrease in body weight gain and food consumption in does. The severity of this finding was dose-and time-dependent. Addition findings noted at 100 and 300 mg/kg/day included significant weight loss associated with decrease in food consumption during the dosing period.

Based on these results, the maternal LOEL was 100 mg/kg/day based on mortality, weight loss and decreased food consumption during the treatment period; the NOEL was 30 mg/kg/day.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: At ≥100 mg/kg/day, treatment-related increases in the incidence of abortions were noted.

2. Altered Growth: At ≥100 mg/kg/day, the fetal body weights were significantly lower compared to controls. Therefore, this finding was considered to be indicative of an altered (retarded) growth effect.

3. Developmental Anomalies: At ≥100 mg/kg/day, the incidences of fetuses/litters with hypoplasia of frontal bone, fusion of nasal bone (300 mg/kg/day), and 27th presacral vertebrae increased compared to the concurrent and historical controls.

Based on the above findings, the developmental LOEL and NOEL were 100 and 30 mg/kg/day, respectively.

C. STUDY DEFICIENCY: The following deficiencies were noted:

- The concentration of sperms in saline was not reported.
- Head anomalies were not evaluated by cross sections of fetal heads
- During phase I of the study, because of excessive softening, the phalanges were excluded from skeletal evaluation.
- The uteri from apparently nonpregnant animals were not stained to detect the implantation sites
- The data on uterine weights were not provided and therefore, the corrected body weight gain could not be determined.

However, these deficiencies did not adversely impact upon the outcome of the study results.

S-41311 MUP Acute Oral Toxicity (81-1)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan, Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/17/96, Date
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral Toxicity- Rat OPPTS 870.1100 [§81-1]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750719 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 MUP (Manufacturing Use Product) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0030
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Single-dose Oral Toxicity Study of S-41311 MUP in Rats
AUTHOR:	Y. Misaki
REPORT ISSUED:	May 12, 1992

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 43750719), groups of five male and five female Crj:CD rats were orally administered 1-5 mL/kg b.w. of undiluted S-41311 MUP at dose levels of 0, 1000, 2000, 2600 (females only), 3200, 4000, or 5000 (males only) mg/kg. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. Mortalities occurred at dose levels of ≥4000 mg/kg in males and ≥2000 mg/kg in females. Clinical signs of toxicity were observed in both sexes within 30 minutes following administration and disappeared within 3 days in survivors. These included decreased spontaneous activity, prone position, lateral position, tremor, clonic convulsion, ataxic gait, irregular respiration, excretion of oily substance, urinary incon-tinence, and blotted fur. Animals that died exhibited tremor, clonic convulsion, and irregular respiration and died within 2-4 hours following administration of the test formulation. Transient supression of body weight gain was noted among males and females at ≥2000 mg/kg. **The acute oral LD_{50} for S-41311 MUP was 4500 mg/kg for males and 2400 mg/kg for females.**

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The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

I. MATERIALS

A. Test Material

Name: S-41311 MUP
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: No information available
Purity: 50.5% S-41311
Formulation No.: 5185
Lot No.: 5185P1101
Stability: No information available

For dosing, the test formulation was administered undiluted (1-5 mL/kg) by plastic syringe; the control group was untreated.

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Company, Ltd., Japan
Age: 6 weeks at the start of the study
Weight: Males - 206 to 226 g; Females - 150 to 168 g when dosed
Housing: 2-3 rats of the same sex in aluminum cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum* except 19 hours before dosing and 4 hours after dosing
Acclimation Period: Seven days

II. METHODS

Food was witheld from the animals for about 19 hours prior to dosing. Five male and five female rats were dosed with each test formulation via gavage using a plastic syringe (2 mL) with a flexible catheter attached. The dosing volume was adjusted to give 1-5 mL/kg. The animals were observed for mortality and clinical signs of toxicity at approximately 10 and 30 minutes, 1, 2, and and 4 hours after dosing and once daily for the remainder of the 14-day observation period. Body weights were recorded prior to dosing, on days 1, 3, 5, 7, 10 and 14 days post-dosing, and at death. At the end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

The LD_{50} value was 4500 mg/kg (95% Confidence Limit: 3950 to 5130 mg/kg) for males and 2400 mg/kg (95% Confidence Limit: 1940 to 2970 mg/kg) for females. Clinical signs of toxicity were observed in

following dosing and disappeared within 3 days. These consisted of decreased spontaneous activity, tremor, prone or lateral position, ataxic gait, clonic convulsion, irregular respiration, urinary incontinence, and blotted fur. The body weight gain was significantly lower compared to controls at 2000 and 4000 mg/kg on day 1 and at 3200 mg/kg on days 1, 3 and 5 in males. In females, it was lower at 2000 and 2600 mg/kg on Day 1 and/ or Day 5. Gross necropsy of dead animals revealed perioral blot with saliva, oily material in the stomach, fluid in the uterine horns and autolysis of the intestine; no remarkable treated-related findings were noted during necropsy of surviving animals. The acute oral LD_{50} was 4500 mg/kg for males and 2400 mg/kg for females.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute oral LD_{50} for S-41311 MUP in rats was greater than 4500 mg/kg for males and 2400 mg/kg for females.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-1) for an acute oral toxicity study in rats.

S-41311 MUP Acute Dermal Toxicity (81-2)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy Date 7/17/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity- Rat OPPTS 8700.1200 [§81-2]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750721 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 MUP (Manufacturing Use Product) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0031
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Single-dose Dermal Toxicity Study of S-41311 MUP in Rats
AUTHOR:	Y. Misaki
REPORT ISSUED:	May 12, 1992

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 43750721), five male and five female Crj: CD rats each received dermal applications of S-41311 MUP at a dose of 2000 mg/kg for 24 hours. A control group was untreated. The animals were observed for mortality and clinical signs of toxicity for 14 days post-dosing. There were no mortalities, clinical signs of toxicity, body weight changes or gross pathology observed in either sex. **The acute dermal LD_{50} for S-41311 MUP in male and female rats was greater than 2000 mg/kg.**

The study is classified as Acceptable with a **Toxicity Category III** and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rats.

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S-41311 MUP Acute Dermal Toxicity (81-2)

I. MATERIALS

A. Test Material

Name: S-41311 MUP
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: No information available
Purity: 50.5% S-41311
Lot No.: 5185P1101
Stability: No information available

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Company, Ltd., Japan
Age: 6 weeks at the start of the study
Weight: Males - 234 to 268 g; Females - 174 to 194 g when dosed
Housing: 2-3 rats of the same sex in stainless cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum*
Acclimation Period: Quarantine over 7 days and acclimatized over 2 days

II. METHODS

One day prior to dosing, the backs of all the animals were clipped, exposing an area of approximately 10% of the total body surface. On the day of dosing, a dose (2 mL/kg) of 2000 mg/kg of undiluted test material was applied on the shaved area (30 cm^2) on the skin using a plastic syringe (2 mL). The treated area was covered with a gauze patch which secured with a surgical tape wrapped around the trunk. Twenty-four hours after the application, the treated skin was wiped with cotton dipped in diethyl ether to assess the skin reaction. The control group received no treatment. The animals were observed for mortality and clinical signs of toxicity at approximately 10 and 30 minutes, 1, 2, and 4 hours after dosing and once daily for the remainder of the 14-day observation period. Body weights were recorded prior to dosing, on days 1, 3, 5, 7, 10 and 14 days post-dosing, and at death. At the end of the observation period, all animals were sacrificed and necropsied.

III. RESULTS

The amount of test substance/area covered approximately 10% of the body surface area. No mortalities and clinical signs of toxicity were observed. Therefore, the estimated LD50 value was greater than 2000 mg/kg for male and female rats. There were no treatment-related changes in body weight gain in either sex. There were no dermal reactions at the site of application and at necropsy, no treatment-related findings were noted. The acute dermal LD_{50} was greater than 2000 mg/kg.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute dermal LD_{50} for S-41311 MUP in male and female rats was greater than 2000 mg/kg.

The study is classified as **Acceptable** with a **Toxicity Category III** and **satisfies** the requirements (81-2) for an acute dermal toxicity study in rats.

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S-41311 MUP Acute Inhalation Toxicity (81-3)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/17/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy Date 7/17/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation Toxicity- Rat OPPTS 8700.1300 [§81-3]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750723 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 50% MUP (Manufacturing Use Product) Synonym: Imiprothrin
STUDY NUMBER:	SGT-30-0064
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Acute Inhalation Toxicity Study of S-41311 50%MUP in Rats
AUTHOR:	T. Yamada
REPORT ISSUED:	December 26, 1993

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID # 43750723), five male and five Sprague-Dawley rats per group were exposed whole-body to mist aerosols at concentrations of 2.81, 3.62 or 4.43 mg/l of S-41311 50%MUP for four hours. The animals were observed for 14 days. Mortalities were noted at all exposure levels; the estimated LC_{50} values were between 3.62-4.43 mg/L for males and 2.81-3.62 mg/L for females. Clinical signs were noted at all exposure levels and in both sexes beginning 1/2 hour after initiation of exposure and included ataxic gait, tip toe gait, ocular discharge and wet fur. In addition, at 3.62 mg/L, hypersensitivity and tremor were noted. These signs disappeared by Day 7 with the exception of loss of hair and erosion in one male that lasted until Day 14. The body weight gain was lower compared to air controls in males and females at 2.81 mg/L and in males at 3.62 mg/L on Day 3; the body weights returned to normal thereafter. No treatment-related gross pathological findings were observed. The mean nominal concentrations were 8.22, 23.5 and 48.2 mg/L for the

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atmospheric concentrations of 2.81, 3.62 and 4.43 mg/L, respectively. The MMAD of mist particles ranged between 3.19-3.75 μm; the GSD range was 1.87-1.92. **The acute inhalation LC_{50} for S-41311 50%MUP in male and female rats was >2 mg/l.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-3) for an acute inhalation toxicity study in rats.

I. MATERIALS

A. Test Material

Name: S-41311 50%MUP
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: Clear, yellow-orange oily liquid (MRID# 437507 22)
Purity: 50.6% S-41311
Lot No.: 5185CES3
Stability of compound: Test material was stable when refrigerated

B. Test Animals

Species: Crj: CD rats
Source: Charles-River Japan, Inc
Age: 6 weeks at the start of the study
Weight: Males - 246 to 276 g; Females - 165 to 196 g when dosed
Housing: 2-3 rats of the same sex in aluminum cage
Environmental Conditions: Temperature: 24±2^0 C
Relative Humidity: 55±10%
Photoperiod: 12 hours light/dark
Air Changes: ≥10/hour
Food and Water: Sterilized CRF-1 Pellet diet (Oriental Yeast Co., Ltd.) and filtered tap water *ad libitum* except during dosing and until 4 hours after dosing
Acclimation Period: Quarantine over 7 days and acclimatized for 1 day

II. METHODS

Exposure Chamber

A five-compartment wire-mesh cage (floor space: 215 cm^2; height: 14 cm) was placed in an exposure chamber. The exposure chamber had a volume of 0.53 m^3. During exposure, five rats were housed in each cage (1 animal/pen; 5 pens/cage)

Atmosphere Generation and Monitoring

Food and water were withheld from the animals during exposure period. The animals were exposed to the test article aerosols by whole-body exposure. The undiluted test material was pumped using a tube pump (TPC-5) into an atomizer (AKI Jet 04) and sprayed under compressed air. The dose administered was expressed as the rate of injection of test material into the atomizer. The aerosols were delivered to the exposure chamber; the chamber air was led to the exhaust port at a rate of 115 L/min and the pressure inside the chamber was maintained at a constant level. During exposure period, the temperature, relative humidity, air flow rate and pressure were monitored at the start of exposure and at 30 minutes as well as at

1, 2, 3, and 4 hours thereafter. A diagram of the test system is attached to the DER.

Analytical Chemistry

The concentration of the chemical in the test atmosphere was determined by HPLC at 1 and 3 hours after the start of exposure. Samples were collected through the sampling line of the chamber in a glass column packed with silica gel and a total of 100 L of chamber air samples was collected at a rate of 15 L/min for approx. 6 minutes using an air-sampler (D-80 RG) equipped with a flow meter. S-41311 50%MUP, collected on silica gel and extracted with acetone, was quantified by HPLC. The actual test concentration in the chamber was calculated using the value obtained from the analysis and the amount of air collected. The nominal test concentrations were obtained by dividing the total volume of the test aerosol consumed during exposure with the total amount of air flow into the chamber.

Time to equilibrium was 4 minutes.

Particle Size Distribution

An Andersen air sampler (Model AN-200) was used to determine the particle size distribution of the test atmosphere twice during the exposure period. The mean MMAD (median aerodynamic diameter) of the mist particles and GSD (geometric log-standard deviation) were estimated using Probit analysis.

Animal Treatment

Five male and five female rats per group were exposed to a 4-hour whole-body exposure at actual concentrations of 2.81, 3.62 or 4.43 mg/L; the control group was exposed to air. Observations for mortality and clinical signs of toxicity were made at 30 minutes and hourly intervals during exposure and after exposure on day 1 (up to 4 hours), and then once daily during the 14-day observation period. The animals were weighed prior to exposure and at 3, 7 and 14 days following the exposure, and at death. At the end of the study, all the surviving animals were sacrificed and necropsied.

III. RESULTS

The calculated nominal concentrations of S-41311 50%MUP were 8.22, 23.5 and 48.2 mg/L for groups exposed to actual aerial concentrations of 2.81, 3.62 and 4.43 mg/L, respectively. The corresponding MMAD of the test aerosols ranged from 3.19 to 3.23 μm, 3.66 μm and 3.31 to 3.75 μm, respectively, and the GSD for these groups ranged from 1.88, 1.87 to 1.92 and 1.88 to 1.91, respectively.

Mortalities occurred at all exposure levels. The following number of animals died during the exposure: 1 male in 2.81 mg/L group, 1 male and 3 females in the 3.62 mg/L group and 4 male and 5 females in the 4.43 mg/L group. The LC_{50} value was estimated to range

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between 3.62-4.43 mg/L for males and 2.81-3.62 mg/L for females. Clinical signs of toxicity were observed in both sexes at all exposure levels within 1 hour of the initiation of exposure and included muscular fibrillation, nasal discharge, salivation and lacrimation. Additional signs were noted in one or both sexes after the termination of exposure and consisted of decrease in spontaneous activity, ataxic gait, tip toe gait, wet fur, ocular discharge, urinary incontinence, irregular respiration and red material around snout (in males) at all exposure. At 3.62 mg/L, hypersensitivity was noted in males; all clinical signs disappeared by Day 7 with the exception of loss of hair noted on day 12 and erosion on Day 13 in one male; this persisted until Day 14. In addition bradypnea and closed eyelids were observed in one male that survived the exposure at 4.43 mg/L but was found dead on Day 1. Males and females at 2.81 mg/L and males at 3.62 mg/L had lower body weight gains compared to air controls on day 3. However, the body weight gain returned to normal thereafter. No treatment-related gross pathological findings were noted at necropsy.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The acute inhalation LC_{50} for S-41311 50%MUP was >2 mg/L (limit concentration) for male and female rats.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-3) for an acute inhalation toxicity study in rats.

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Pages _____ through _____ are not included in this copy.

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_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

S-41311 MUP Primary Dermal Irritation Study (81-5)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/19/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/17/96 Date
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Dermal Irritation- Rabbit OPPTS 8700.2500 [§81-5]
EPA ID NUMBERS:	DP BARCODE: D222183 P. C. CODE: 004006 MRID NUMBER: 43750725 SUBMISSION No.: S498997
TEST MATERIAL:	S-41311 MUP (Manufacturing Use Product) Synonym: Imiprothrin
STUDY NUMBER:	SGT-20-0014
TESTING FACILITY:	Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Osaka, Japan
SPONSOR:	Sumitomo Chemical Co., Ltd., Osaka, Japan
TITLE OF REPORT:	Primary Eye and Skin Irritation Tests of S-41311 MUP in Rabbits
AUTHOR(S):	T. Nakanishi
REPORT ISSUED:	February 12, 1992

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID # 43750725), 0.5 mL of undiluted S-41311 MUP was topically applied to a clipped skin area of each of six New Zealand white rabbits (3/sex) for four hours. The treated areas were examined for signs of dermal irritation (edema and erythema) and scored after 30 minutes and at 24, 48 and 72 hours post-treatment. No evidence of erythema or edema was observed in treated rabbits at any of the time periods. **The study demonstrated that S-41311 MUP is non-irritating to the rabbit skin.**

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for a primary dermal irritation study in rabbits.

I. MATERIALS

A. Test Material

Name: S-41311 MUP
Chemical Name: [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl] methyl (1R)-cis-trans-chrysanthemate
Synonym: Imiprothrin
Description: Liquid
Purity: 50.5% S-41311
Formulation No.: 5185
Lot No.: 5185P1101
Stability of compound: No information available

B. Test Animals

Species: New Zealand white rabbits
Source: Kitayama LABES, Kyoto, Japan
Age: 10 weeks
Weight: Males and Females - 2.39-2.60 kg at dosing
Housing: Individually in aluminum cages
Environmental Conditions: Temperature: 22±2°C
Relative Humidity: 55±15%
Photoperiod: 12 hours light
Air Changes: ≥10/hour
Food and Water: 100 g/day of RC-4 diet from Oriental Yeast Co., Ltd, Tokyo and water *ad libitum*
Acclimation Period: 14 days quarantine period followed by 17 days of acclimation

II. METHODS

Approximately 24 hours before treatment, the dorsal fur of each rabbit was clipped (the area size was not specified). On the day of dosing, 0.5 ml of the test material impregnated on a lint patch (2.5 x 2.5 cm), was applied to the clipped dorsal skin and secured in place with a surgical tape. At the end of the 4-hour exposure, the patches were removed and the treated sites were wiped with cotton soaked in acetone. The areas were examined for signs of dermal irritation and scored after 30 minutes and at 24, 48 and 72 hours post-application. A copy of the Draize grading scale is attached to the DER. The skin irritation potential was determined from the primary skin irritation score obtained.

III. RESULTS

No skin reactions were observed in treated rabbits at any of the observation period. The primary skin irritation score was 0.0. The study demonstrated that S-41311 MUP was non-irritating to the rabbit skin.

IV. COMPLIANCE

The following compliance documents were submitted: 1) signed statement by the sponsor indicating that the study was conducted in accordance with GLP Regulations; 2) signed Quality Assurance statement by the testing facility; 3) signed statement by the sponsor claiming no data confidentiality.

V. CONCLUSIONS

The study demonstrated that S-41311 MUP is non-irritating to the rabbit skin.

The study is classified as **Acceptable** with a **Toxicity Category IV** and **satisfies** the requirements (81-5) for a primary dermal irritation study in rabbits.

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Application denied

Page 1 is not included in this copy.

Pages _____ through _____ are not included in this copy.

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_____ Identity of product inert ingredients.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

S-41311 MUP Dermal Sensitization Study (81-6)

Reviewed by: Sanjivani B. Diwan, Ph.D. Sanjivani Diwan Date: 7/30/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y M. Ioannou Date: 7/31/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization - Guinea Pig
OPPTS 8700.2600 [§81-6]

DP BARCODE: D222183
P. C. CODE: 004006
SUBMISSION NO.: S498997
MRID NUMBER: 43750729
TOX CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): Imiprothrin (50% formulation)

SYNONYMS: S-41311 MUP

CITATION: Kosagi S. 1995. Skin Sensitization Test of S-41311 MUP in Guinea Pigs (Maximization Method). Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd., Osaka, Japan. Laboratory Report No. SGT-50-0068 February 9, 1995. MRID 43750729 Unpublished.

EXECUTIVE SUMMARY: In a Magnusson and Kligman test (MRID # 43750729), a group of 20 male Hartley guinea pigs received intradermal injections of 5% S-41311 MUP in corn oil and 10% S-41311 MUP in Freund's complete adjuvant (FCA) and distilled water followed by dermal application of undiluted S-41311 MUP for 48 hours during the induction phase. Two weeks later during the challenge phase, a patch covered 5% and 25% S-41311 MUP in corn oil or corn oil alone was applied at the test sites.

The positive control group (5 males) received 0.05% DNCB in corn oil and 0.1% DNCB in FCA and distilled water intradermally and 0.5% DNCB in corn oil dermally during the induction phase. The S-41311 MUP and DNCB non-sensitized groups were treated only during the challenge phase.

No erythema or edema was observed in S-41311 MUP sensitized and non-sensitized animals. DNCB sensitized group showed moderate to severe erythema and slight to severe edema. No skin reactions were noted in DNCB non-sensitized animals. **These results indicate that S-41311 MUP is not a sensitizer in guinea pigs.**

The study is classified as **acceptable** and **satisfies** the requirements (81-6) for a dermal sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality and Flagging statements were provided.

I. MATERIALS

A. MATERIALS:

1. Test Material:
Description: Liquid
Purity: 50.5% S-41311
Lot #: 5185CES3
Formulation #: 5185

2. Vehicle and positive control:

Vehicle: Distilled water; lot # 92B20A;
Corn oil; lot # V3R4952
Freund's Complete Adjuvant (FCA); lot # 46300
Positive control: 2,4-Dinitrochlorobenzene (DNCB)
Lot #: TWG2966
Purity: 98.5%

3. Test Animals: Species: Hartley guinea pigs
Source: Charles River Company, Ltd., Japan
Age and weight at the start of treatment: 3 weeks;
Males - 288-400 kg at dosing
Acclimation period: 7 days quarantine period followed by 4 days of acclimation
Diet: GC-4 Diet (Oriental Yeast Company, Ltd., Tokyo) *ad libitum*
Water: Tap water *ad libitum*
Housing: 5 males per aluminum cage
Environmental Conditions: Temperature: 24±2°C
Humidity: 50±20%
Air Changes: ≥10/hour
Photoperiod: 12 hours light

B. STUDY DESIGN and METHODS:

1. In life dates - start: November 7,1994
end: December 2, 1994

2. Animal assignment and treatment -

The study was conducted using the maximization test of Magnusson and Kligman method.

Preliminary Test

In a preliminary test, guinea pigs (number unspecified) received intradermal injections (0.1 mL/site) of the test substance in corn oil at concentrations of 0.2%, 1% and 5%. In the 5% S-41311 MUP group, slight erythema was observed in one of 3 guinea pigs at 24 and 48 hours after

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groups. When 5%, 10%, 25% and 50% (undiluted) solutions were applied in corn oil under occluded patch for 24 hours, slight erythema was noted in the 10% and 25% dose groups (in 2/3 and 1/3 guinea pigs, respectively, at 24 hours only). In the 50% dose group, slight erythema was noted in 4/6 and 3/6 guinea pigs at 24 and 48 hours, respectively. Based on these results, the 5% and 50% (i.e., undiluted) test concentrations were selected for intradermal injection and epidermal application, respectively, during the main study; 25% and 5% solutions of S-41311 MUP were selected for the challenge dose.

Main study

The animals were assigned to four groups as summarized below.

Groups (No. of animals)	Intradermal induction	Percutaneous induction	Challenge application
S-41311 Sensitized (20)	•FCA* + distilled water •5% S-41311 MUP in corn oil •10% S-41311 MUP in FCA + distilled water	Undiluted S-41311 MUP	•25% S-41311 MUP in corn oil •5% S-41311 MUP in corn oil •Corn oil
S-41311 non-sensitized (20)	•FCA + distilled water •Corn oil •FCA + distilled water	Corn oil	•25% S-41311 MUP in corn oil •5% S-41311 MUP in corn oil •Corn oil
DNCB sensitized (5)	•FCA + distilled water •0.05% DNCB in corn oil •0.1% DNCB in FCA + distilled water	0.5% DNCB in corn oil	•0.5% DNCB in corn oil •Corn oil
DNCB non-sensitized (5)	•FCA + distilled water •Corn oil •FCA + distilled water	Corn oil	•0.5% DNCB in corn oil •Corn oil

Induction Phase

During intradermal induction, six injections in three groups of two per animal, were administered in the shaved area of the suprascapular region (injection site: 2 x 4 cm) as follows:

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S-41311 MUP sensitized group received two injections (at right and one left test site) each of 0.1 ml Freund's adjuvant/saline (1:1) in the upper row; 2 injections each of 0.1 ml of 5% S-41311 MUP dilution in corn oil (0.05% DNCB in DNCB sensitized group) in the middle row; and 2 injections each of 0.1 ml Freund's adjuvant with S-41311 MUP diluted to 10% emulsion with corn oil (0.1% DNCB in FCA and distilled water to DNCB sensitized group) in the lower row.

S-41311 MUP and DNCB non-sensitized animals received similar injections with formulating agent but without the test substance. Skin reactions were recorded 24 hours after beginning of intradermal phase.

During epidermal application (8 days after intradermal injections), 2 x 4 cm lint patch impregnated with 0.2 ml of undiluted S-41311 MUP in corn oil was placed over the shaved test site (0.2 ml of 0.5% DNCB in corn oil in DNCB sensitized group). The patch was secured by dressing for 48 hours. The non-sensitized groups (S-41311 MUP and DNCB), received similar treatment but without S-41311 MUP or DNCB, respectively. Evaluations for signs of dermal irritation were made at 24 and 48 hours post application.

Challenge Phase

Two weeks following the epidermal application, a 2 x 2 cm patch of lint patch impregnated with 0.1 ml of 25% and 5% test material in corn oil was applied to the test site in right flank region. The left flank region was treated with corn oil. The patch was secured in place with surgical tapes for 24 hours in S-41311 sensitized and non-sensitized groups. The DNCB sensitized and non-sensitized groups received 0.1 ml of 0.5% DNCB in corn oil and corn oil alone. After a twenty-four hour exposure period, the application sites were examined at 24 and 48 hours post-dosing using the standard shown below.

Score	Basis of judgement
0	No reaction
1	Slight reaction (with no clear boundary)
2	Moderate reaction (with clear boundary)
3	Severe reaction

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Based on percentage of animals sensitized at 24-hour reading, the test article was assigned to one of the five grades of allergenic potency ranging from weak (Grade I) to extreme (Grade V) according to the standard by Magnusson and Kligman shown below.

Sensitization rate (%)	Grade	Classification
0 - 8	I	Weak
9 - 28	II	Mild
29 - 64	III	Moderate
65 - 80	IV	Strong
81 - 100	V	Extreme

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration -

No skin reactions were observed in S-41311 MUP sensitized and non-sensitized groups.

B. Challenge reactions and duration - Twenty-four and 48 hours after the challenge application, no erythema or edema were noted in S-41311 MUP sensitized and non-sensitized groups at either the 24 or 48-hour observation period.

C. Positive control - For the DNCB sensitized group, 100% of the animals showed positive reactions (moderate to severe erythema and slight to severe edema; severity grade: 1-3) at 24 and 48 hours after patch removal indicating strong sensitization potential. No skin reactions were noted in DNCB non-sensitized group.

E. Deficiencies - The sensitization potential of S-41311 MUP was tested only in male guinea pigs. However, this deficiency does not negatively impact upon the results of the study.

S-41311 MUP Dermal Sensitization Study (81-6)

Reviewed by: Sanjivani B.Diwan, Ph.D. Sanjivani Diwan, Date: 6/5/96
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y. M. Ioannou, Date: 6/6/96
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization - Guinea Pig
OPPTS 8700.2600 [§81-6]

DP BARCODE: D222183 SUBMISSION NO.: S498997
P. C. CODE: 004006 MRID NUMBER: 43750728

TEST MATERIAL (PURITY): S-41311 MUP (50% formulation)

SYNONYMS: Imiprothrin

CITATION: Nakanishi T. 1992. Skin Sensitization Test of S-41311 MUP in Guinea Pigs. Environmental Health Science Laboratory, Sumitomo Chemical Company, Ltd., Osaka, Japan. Laboratory Report No. SGT-20-0020. March 11, 1992. MRID 43750728. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID # 43750728) using the Buehler method, a group of ten male Hartley albino guinea pigs received three topical induction doses of undiluted S-41311 MUP at weekly intervals. Two weeks later during the challenge phase, the animals received topical applications of 0.5 ml undiluted S-41311 MUP.

The positive control group of five males received 1% 2,4-dinitrochlorobenzene (DNCB) in acetone during the induction phase and 0.5% DNCB during the challenge phase. The S-41311 and DNCB non-sensitized groups received treatment during the challenge phase only.

No skin reactions were observed in the test and negative control groups at the 24 and 48 hour examinations. The positive control group showed slight to moderate skin sensitization. The results of this study indicate that S-41311 MUP is not a sensitizer in guinea pigs.

The study is classified as acceptable and satisfies the requirements (81-6) for a dermal sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality and Flagging statements were provided.

I. MATERIALS

A. MATERIALS:

1. Test Material:
Description: Liquid
Purity: 50.5% S-41311
Lot #: 5185P1101
Formulation #: 5185

2. Vehicle and positive control:

Vehicle: Corn oil
Positive control: 2,4-Dinitrochlorobenzene (DNCB)
Lot #: ECQ 4278
Purity: ≥98.5%

3. Test Animals: Species: Hartley guinea pigs
Source: Charles River Company, Ltd., Japan
Age and weight at the start of treatment: Approx. 3 weeks;
Males - 321-419 g at dosing
Acclimation period: 7 days quarantine period followed by 6 days of acclimation
Diet: GC-4 Diet (Oriental Yeast Company, Ltd., Tokyo) *ad libitum*
Water: Tap water *ad libitum*
Housing: 5 males per aluminum cage
Environmental Conditions: Temperature: 24±2°C
Humidity: 55±15%
Air Changes: ≥10/hour
Photoperiod: 12 hours light

B. STUDY DESIGN and METHODS:

1. In life dates - start: January 22, 1992
end: February 21, 1992

2. Animal assignment and treatment -

The study was conducted using the Buehler method.

Preliminary Test

In a dose range-finding study, no irritation was observed in guinea pigs (number unspecified) receiving dermal application of undiluted S-41311 MUP in corn oil. Based on this observation, undiluted S-41311 MUP

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was applied during the induction and the challenge phases of the main study.

Main Study

The animals were assigned to four groups as summarized below.

Group	Number of Animals	Induction Concentration	Challenge Concentration
S-41311 sensitized group	10	Undiluted S-41311 MUP	Undiluted S-41311 MUP
S-41311 non-sensitized group	10	--	Undiluted S-41311 MUP
DNCB sensitized group(Positive control)	5	1% DNCB in acetone	0.5% DNCB in acetone
DNCB non-sensitized group	5	--	0.5% DNCB in acetone

Induction Phase

A total of three weekly induction doses were applied using the procedure described below. For the test material, all three induction applications were made to the clipped area of the flank region. A lint patch (1.5 x 1.5 inch) impregnated with 0.5 ml of the undiluted S-41311 MUP or 1% DNCB in acetone was applied to the flanked skin. The patch was secured in place with a surgical tape. After six hours of exposure, evaluations for signs of skin irritation (erythema and edema) were made, at 24 and 48 hours post application, using the following standard:

Grade	Reaction to Treatment
0	no reaction
1	slight reaction (with no clear boundary
2	moderate reaction with clear boundary
3	Severe reaction

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Both the S-41311 MUP and DNCB non-sensitized groups received similar treatment but without the test material or DNCB.

Challenge Phase

Two weeks following the last induction dose, the challenge doses of undiluted S-41311 MUP were applied to the test sites of both the sensitized and non-sensitized animals using the same procedure as in the induction phase. DNCB sensitized and non-sensitized groups received 0.5 ml of 0.5% DNCB in acetone in the same manner. The application sites were examined at 24 and 48 hours post-dosing for the severity of erythema and edema.

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration -

No skin reactions were observed in S-41311 MUP sensitized and non-sensitized animals.

B. Challenge reactions and duration -

Twenty-four and 48 hours after the challenge application, no skin reactions were noted in S-41311 MUP sensitized and non-sensitized animals.

C. Positive control - For the DNCB sensitized positive controls, 100% of the animals showed positive reactions (severity grade: ≥ 1) indicating skin sensitization potential. These animals when challenged with 0.5% DNCB, exhibited moderate erythema and slight to moderate swelling after 24 hours, and slight to moderate erythema and slight swelling after 48 hours. No skin reactions were observed in DNCB non-sensitized animals. All animals gained weight during the course of the study.

E. Deficiencies -

The sensitization potential of S-41311 MUP was tested in male guinea pigs only. However, this deficiency does not negatively impact upon the results of the study.